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Caring for adult survivors of childhood cancer

Blaauwbroek, Ria

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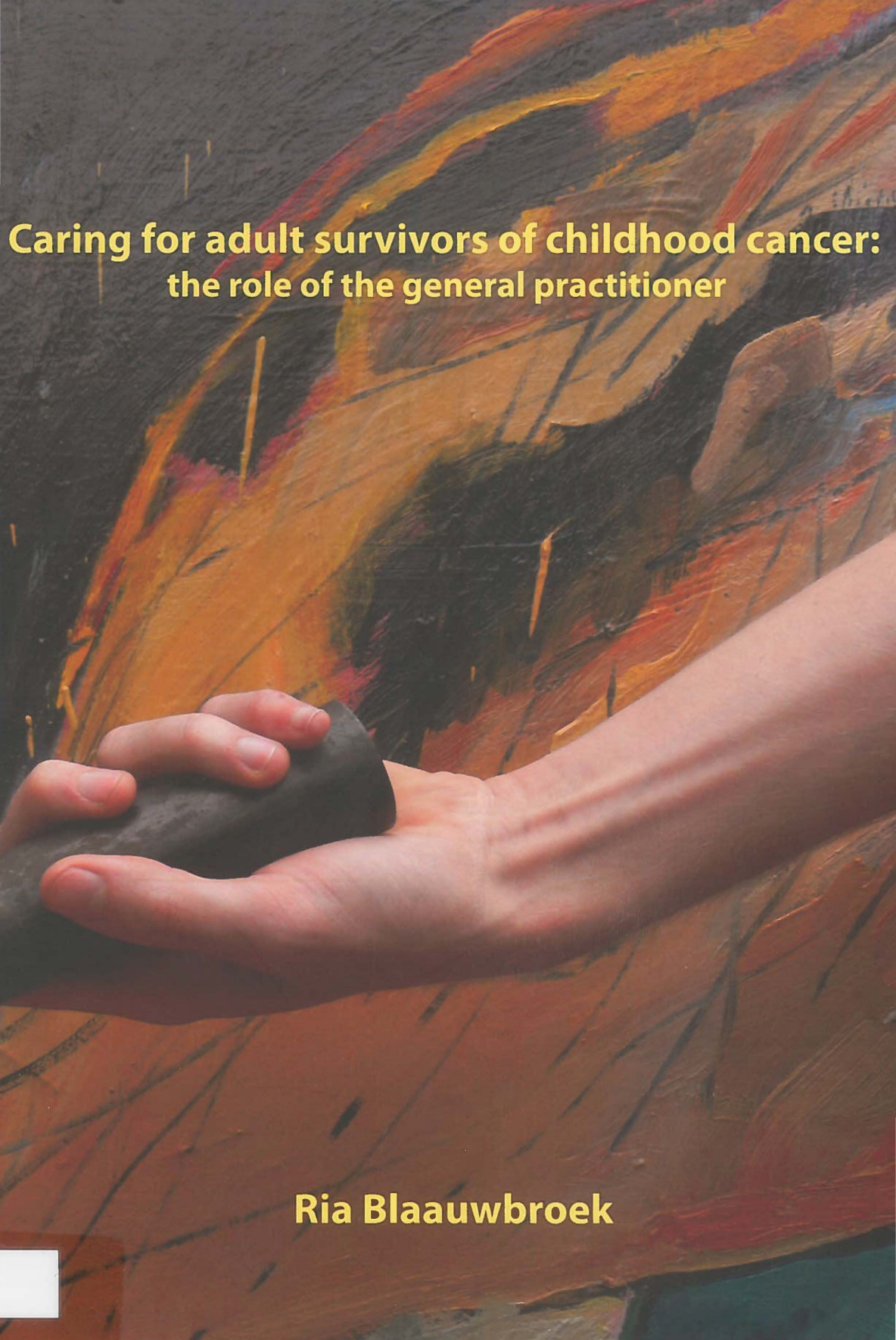
Caring for adult survivors of childhood cancer:
the role of the general practitioner
Ria Blaauwbroek

Caring for adult survivors of childhood cancer:

the role of the general practitioner

Stellingen

behorende bij het proefschrift
Caring for adult survivors of childhood cancer:
the role of the general practitioner

1. "Cure is not enough" (Giulio D'Angio) but we should not forget there is not yet enough cure.

2. Het is zinvol om overlevenden van kinderkanker die niet gecontroleerd worden, terug te roepen voor onderzoek op late effecten. *Dit proefschrift*

3. Overlevenden van kinderkanker die meer dan 20 jaar geleden zijn behandeld hebben meer ernstige late effecten en een slechtere kwaliteit van leven dan overlevenden die minder dan 20 jaar geleden zijn behandeld. *Dit proefschrift*

4. Vermoeidheid bij overlevenden van kinderkanker verbetert door het stimuleren van "huis, tuin en keuken" beweging met feedback van een stappenteller. *Dit proefschrift*

5. Lange termijn follow-up voor volwassen overlevenden van kinderkanker kan goed uitgevoerd worden door huisartsen in samenwerking met kinderoncologen.
Dit proefschrift

6. Het verplichte ontslag als werknemers 65 jaar worden, moet worden omgezet in een recht om op die leeftijd met pensioen te gaan.

7. Kennis van vroegere ziekte en behandeling bevordert de bewustwording van het risico op eventuele late effecten van behandeling. *Dit proefschrift*

8. Alles wat in de vorige eeuw is misgegaan is moeders schuld. (Peter Bügel)

9. Van goed onderwijs kun je nooit te veel uren krijgen, van slecht onderwijs is elk uur er één te veel. (Rene Cuprus, publicist Volkskrant, 2007)

10. Als een rommelig bureau het teken is van een rommelige geest, waar staat een leeg bureau dan voor? (Albert Einstein)

11. Als het niet vastloopt, dan is het geen computer. (Willem Kamps)

12. Of iemand politiek progressief of conservatief is, hangt samen met de manier waarop het brein met angst omgaat.(Professor Kevin B. Smith, Science 2008)

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Ria Blaauwbroek

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Coverontwerp:
De cover is ontworpen door Niels Kruyt en Bart Lanting en staat symbool voor de overstap naar de volwassen zorg van (jong) volwassenen die genezen zijn van kinderkanker en voor het belang van samenwerking hierbij.

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Caring for adult survivors of childhood cancer:

the role of the general practitioner

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CHAPTER 1

General introduction and outline of the thesis

INTRODUCTION

Childhood cancer is a rare disease. In the Netherlands there are no more than 400–500 new cases of cancer in children under the age of 16 each year. Around 1950, the five-year survival rate for cancer diagnosed in children aged 0–14 was less than 20%. Between 1995 and 2000 this rate increased to 75%.[1] The increase in survivability of childhood cancer has translated into a growing population of young adult survivors. At the same time it has become clear that the success of cure has not come without cost. The adverse late effects of the treatment for childhood cancer may present themselves after many years, sometimes after these children reach adulthood. Studies estimate that at least two-thirds of adults who survived childhood cancer have had at least one late complication and approximately one-third have had serious or life-threatening complications.[2-4]

Childhood cancer survivors have an excess risk of mortality due to relapse of the primary cancer or therapy-related secondary cancers and late complications, mainly cardiac or pulmonary disease.[5,6]

Much knowledge about these late effects has been obtained from two large cohort studies. In the US the Childhood Cancer Survivor Study (CCSS) started in 1993, and in the UK the British Childhood Cancer Survivor Study (BCCSS) started in 1998. Both studies suffer from their reliance on questionnaires completed by survivors or family members.

The pathophysiology of many late effects has not yet been sufficiently explained. Building on the experiences of adult breast cancer survivors, Maccormick proposed the hypothesis that chemotherapy accelerates the natural aging process. Probably caused by tissue damage by free radicals, DNA damage, decreased telomerase activity resulting in premature apoptosis or damage to neuro-endocrine and immunological processes.[7] Whether this is also the case in children treated with chemotherapy is not yet clear, nor are the clinical implications.

According to Bleyer's calculation, one person in every 1000 aged between 15 and 45 was a survivor of childhood cancer in 2000. This will reach one in every 250 in 2010.[8] Along with the steadily growing number of childhood cancer survivors, general practitioners (GPs) will be increasingly confronted with the problems of late effects in childhood cancer survivors.

Follow-up

For a long time, it was common practice to discharge paediatric cancer patients after a disease-free interval of approximately ten years. Young children continued follow-up until about the age of 18–20. Today, paediatric oncologists worldwide believe that a systematic plan for lifelong screening and surveillance should be offered to all survivors.[9]

To reduce the morbidity of late effects it is important to detect and treat diseases as early

as possible, preferably at a subclinical stage. The scope of late effects has not yet fully been mapped, as the oldest survivors are now between the ages of 30 and 40 and we do not yet know the health risks for the elderly.

Therefore, follow-up should be combined with reliable registration and research into late complications and risk factors. Survivors of childhood cancer need periodic assessments and information about the health risks, combined with lifestyle counselling (for example, regarding smoking, alcohol and exercise) to decrease further damage.

To date, not all survivors of childhood cancer have received the recommended follow-up care. Oeffinger et al. (2004) showed that in the US only 31% and 17% of the survivors aged 18 and 35 respectively were still in follow-up.[10] Over the same period in the UK, fewer than half of the survivors were in follow-up.[11] Recently in the Netherlands, the registration of late effects (LATER) was initiated. This is a nationwide registration of patient characteristics, treatments and follow-up data for all childhood cancer survivors in the Netherlands. These data are obtained by screening the complete cohort of 5- year survivors at the LTFU clinics. Survivors discharged from follow-up years ago are being recalled to the LTFU clinics. Once this cohort is complete, this LATER project can provide more insight into the risk factors and the prevalence of the various late effects, which could lead to adjustments of future treatment protocols and primary prevention in future patients.

Not all health care providers are in favour of keeping all childhood cancer survivors in lifelong follow-up. Some believe that the majority of childhood cancer survivors will do well and they emphasize that long-term follow-up for these patients might have negative consequences. The psychological impact of requesting patients to return time and again could suggest the presence of ongoing abnormality, thus providing negative reminders of previous illness. Moreover, routine follow-up is expensive and these costs may not be justified with the current lack of strong evidence-based data.[12] Some propose that the most efficient method of follow-up care consists of informing patients of their risks and having them see their GP as soon as they have any problems. For this purpose a written summary of disease and treatment for every survivor could be helpful.

It is uncertain whether this model is applicable to the long-term future. In the Netherlands most visitors to the LTFU clinics receive a short written summary with information composed by the Dutch Childhood Cancer Parent Organisation (VOKK). A survey of visitors of the LTFU clinic in Groningen revealed that more than half did not remember having received this information booklet or had lost it. The costs argument needs further study – it could also be that detecting and, if possible, treating late effects at an early stage is cost effective. For that matter, the costs aspect should play a role in deciding which model of follow-up is preferable.

Guidelines

Based upon the assumption that follow-up is required and significant, the question arises as to who is best suited to provide this care and where the best place for follow-up is. Much effort is being invested in the development of guidelines for assessment of the late effects of cancer treatment, such as the guidelines published by the US Children's Oncology Group, the UK Children's Cancer and Leukaemia Group (CCLG) and the Scottish Intercollegiate Guidelines Network (SIGN). These guidelines differ from each other, probably due to the social and cultural differences between the countries. The American guidelines (www.survivorshipguidelines.org) provide for more frequent and more extensive investigations than the English or Scottish guidelines (www.ukccsg.org;www.sign.ac.uk).

In the Netherlands the Late Effects task group of the Dutch Childhood Oncology Group (DCOG) has almost completed evidence-based Dutch guidelines, based on already existing foreign guidelines, literature and expert opinion.[13]

Models of follow-up

Increasing knowledge of late effects in childhood cancer survivors resulted in many paediatric cancer centres starting separate long-term follow-up clinics (LTFU). Ideally, the team in such a clinic consists of paediatric oncologists, social workers, psychologists and consultants, such as cardiologists, nephrologists and endocrinologists. This could be the ideal follow-up model for children up to age 18 – but what of adulthood? Where and by whom can adult survivors be followed? Are they still to be seen in the LTFU clinics led by paediatric oncologists? Is there a transition model that provides transition to internists or GPs specializing in late effects?

In this thesis we will try to determine whether there is a role for the GP in the follow-up of adult childhood cancer survivors. Worldwide experiments have started with different models for the follow-up of adult survivors, every one of which possesses its own advantages and disadvantages.[12,14-18] So far, long-term follow-up of childhood cancer survivors has been mainly organized by paediatric oncologists, with general practitioners involved only rarely. Yet paediatric oncologists are ill-equipped to investigate adult patients, highlighting the need for new models to be developed.

Goldsby suggests four possible models for long-term follow-up care.[12]

1 Patient driven: The survivor is given a summary of therapy and informed of the risks, and seeks care if necessary.
2 Primary care provider driven: The survivor and the GP are given a summary of therapy and the associated risks and the survivor is followed in the local community.
3 Paediatric oncologist driven programme: The survivor is given a summary of therapy and the long-term follow-up is directed by a paediatric oncologist with an interest in the late effects of treatment.

4 Adult medicine driven programme: Survivor is given a summary of therapy and the long-term follow-up is directed by an adult medical provider with an interest in late effects. This might be an adult oncologist, general medical physician or a general practitioner.

Each model has its advantages and disadvantages, which are described in Table 1.

Table 1.Four models of long-term follow-up care (LFTU).

Type of LTFU	Description	Advantages	Disadvantages
(1) Patient driven	Survivor is given a summary of therapy and educated regarding risks.	Survivor is informed and seeks care as they see fit.	Greatest potential for lack of follow-up. May miss opportunity to treat conditions early and educate survivor about newly identified issues regarding late effects. Minimizes research opportunity.
(2) Primary care provider (PCP) driven	Survivor and PCP are given the summary of therapy and associated risks.	Survivor is followed in the local community.	PCP may not stay current with follow-up recommendations and may not have the necessary expertise to recognize potential late effects. Survivor may change PCPs. Limits research opportunity.
(3) Pediatric oncologist driven programme	Survivor is given a summary of therapy and LTFU directed by pediatric oncologist with interest in late effects.	Care providers with expertise in and familiar with late effects. Bond with survivor already established. Established referral experts. Maximizes research opportunity.	As survivors age, other issues arise that may be better followed by adult medicine. Maximizes research opportunity. May not be convenient for the survivor.
(4) Adult medicine driven programme	Survivor is given a summary of therapy and LTFU directed by adult medicine provider with interest in late effects.	Care providers with expertise in and familiar with late effects. Established referral experts. Maximizes research opportunity.	Requires an adult oncologist, internal medicine, or family practice physician to develop specialized clinical interest in late effects of childhood cancer therapy. Interest in this area of medicine may increase as this population grows. Also requires survivors to see yet another healthcare provider, which may deter follow-up. May not be convenient for the survivor.

*Goldsby RE, Ablin AR. Surviving childhood cancer; now what? Controversies regarding long-term follow-up. Pediatric Blood and Cancer 2004;43:211-214.

However, as long as the individual patient receives the appropriate level of care, more than one model may be appropriate.[19]

Because of the initial bond made with the survivor, paediatric oncologists might be preferable. Additionally, they have a detailed understanding of the treatment protocols and may be best placed to identify the risks of late effects due to the therapy. However, they are not trained to deal with many of the issues and clinical conditions seen in the adult population. When survivors age, co-morbidity is more likely to be present and a physician with a recognized understanding of adult health-related issues should provide the care. This could be an adult oncologist, an internist or a GP with a special interest in the late effects of childhood cancer therapy. This setting in a tertiary centre maximizes research opportunities, but individuals may be reluctant to continuously return to this

kind of clinic for routine visits due to psychological, cost or time-related factors. Given that there is an ever enlarging population of survivors, the costs of running such a clinic will rise indefinitely and there may also be a capacity problem. Cooperation with the local GP could remove some of these barriers but the heterogeneity of the care would increase, which could hinder the collection of accurate follow-up care data.
The survivors of childhood cancer are a heterogeneous group with heterogeneous health problems that do not fit one speciality. A doctor providing long-term care to adult survivors needs to have knowledge of late effects, needs to be a generalist and needs to have an eye for psychosocial problems. Care depends on the lines of communication between an informed patient, the local GP and the long-term follow-up expert at the LTFU clinic, and the availability of specific guidelines for follow-up – if the local GP is capable of providing the necessary ongoing follow-up - needs further study. The most challenging aspect of this approach would be the collection of long-term follow-up data for the purposes of research.

The present situation in the Netherlands

In the Netherlands, different models of follow-up for adult survivors of childhood cancer are being explored. In some centres a specialist for adults, for example, an adult oncologist or internist provides the care. The University Medical Center Groningen (UMCG) has explored a shared-care model of paediatric oncology and general practice. This model has the paediatric oncologist cooperate with the local GP, and a GP working at the LTFU clinic coordinates the follow-up from both a research and clinical perspective.
The local GP is informed of the possible health risks to the patient and the appropriate guidelines are communicated prior to the survivor's visit to his/her GP. The GP is required to return the results of the required tests to the LTFU clinic. Clear advantages for follow-up care given by local family doctors rather than by hospital staff include less patient travel, shorter waiting times, better patient familiarity with surroundings (i.e. the doctor's practice) and less stigmatization. As survivors grow older and possibly develop additional chronic age-related illnesses, access to care in the context of total health needs becomes more useful.
If necessary, the GP can refer survivors to an expert such as an endocrinologist, cardiologist or lung specialist. Being involved in a shared-care model for the follow-up of adult survivors of childhood cancer will increase the GP's general knowledge of the late effects of cancer treatment.

Tailor-made follow-up

Since survivors of childhood cancer are a very heterogeneous group, Wallace et al.[15] suggested that follow-up should be organized at three levels, according to the patient's

individual risk profile. Patients with no or very low risk could be followed by questionnaires or telephone follow-up. High-risk patients should be given annual follow-up in a LTFU clinic. The local GP could play a role in the follow-up for the remaining patients, who are classified as a medium-risk group.

Aims of the thesis

The general aims of the thesis are

1 To investigate late effects in adult childhood cancer survivors
2 To study a shared-care model for long-term follow-up for adult survivors of childhood cancer

In Chapters 2 and 3 we show the frequency of late effects and the grade of severity in adult childhood cancer survivors, and how the presence of these late effects influences their Quality of life (QoL).

Chapter 4 will report the findings of our investigation into what adult survivors who visit the LTFU clinic in Groningen know about their disease and their late effects risks. In addition, the degree of knowledge possessed by survivors who were recalled to the LTFU clinic and were visiting the clinic for the first time will be compared with the knowledge possessed by survivors who had been visiting the LTFU clinic on a regular basis.

Chapter 5 will report the results of a simple home-based counselling physical activity programme, using pedometer feedback on fatigued adults who survived childhood cancer.

Cancer related fatigue may occur long after the treatment of childhood cancer has ended with negative effects on quality of life. Current revalidation programmes that include the stimulation of physical activity have a positive effect, but are intensive and time consuming. This makes them less suitable for young survivors of childhood cancer, who often find themselves at the beginning of a professional career or with a family to care for.

Chapter 6 will present the results of our investigation into the willingness of GPs who had followed a postgraduate course on the late effects of cancer treatment, to participate in a shared-care model for follow-up of adult survivors of childhood cancer, as well as what their requirements would be when they participated.

Chapter 7 answers the following questions

- Is low-frequency follow-up at the LTFU clinic in combination with regular follow-up by the survivor's own GP feasible?
- Is a shared-care model compatible with the collection of data and the need for registration of any adverse late effects of childhood cancer treatment?
- How is a shared-care model evaluated by survivors and by GPs?

Chapter 8 contains the general discussion, conclusions and recommendations.

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CHAPTER 2

Health-related quality of life and adverse late effects in adult (very) long-term childhood cancer survivors

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ABSTRACT

Purpose: 1.To assess health-related quality of life (HRQoL) of adult long term (up to 20 years) and very long term (>20 years) childhood cancer survivors, compared to the HRQoL of an age matched Dutch population sample.
2.To evaluate the impact of cancer-related adverse late effects on the functional, psychological and social health of childhood cancer survivors.

Method: The RAND-36 was used to assess HRQoL in all adult (≥ 18 years) survivors who had attended the long-term follow-up clinic since 1995. The survivors were divided into two groups based on the length of follow-up: Group LF (long term follow-up, follow-up ≤ 20 years, n = 129) and Group VLF (very long-term follow-up, follow-up >20 years, n = 184). Data on diagnosis, treatment and complications were obtained from medical records. Late effects were graded using the CTCAEv3.

Results: The RAND-36 was completed by 313 (86.2%) out of 363 eligible patients. Except for higher scores on the subscale Bodily pain, LF patients did not differ significantly on the RAND-36 subscales from the population sample; VLF patients had significant lower scores on the subscales Physical functioning (P = 0.003), Social functioning, Vitality and General health perception (P < 0.001). Significantly more VLF patients (P < 0.001) had severe (grade 3 and 4) late effects (47.8%) compared to LF patients (27.9%). Female gender and especially psycho-social late effects were inversely related to HRQoL.

Conclusion: Childhood cancer survivors who were diagnosed more than 20 years ago have lower scores on the RAND 36, and have significantly more severe late effects than those diagnosed more recently. Patients with longer follow-up are more likely to become lost to follow-up. Time has come to establish new models of care for adult childhood cancer survivors, which are more flexible and appropriate to the needs of adult childhood cancer survivors.

1. INTRODUCTION

Advances in paediatric cancer therapy have led to long-term survival of more than 70% of patients treated.[1,2] Consequently, there have been a growing number of childhood cancer survivors in the last few decades. Along with the impressive gains in survival, negative long-term consequences related to the disease or its treatment, i.e. adverse late effects, have been acknowledged in the recent literature as well. These late effects can seriously impair the survivors' overall health. It is estimated that physical and/or psychosocial complications will develop in as many as two thirds of these young adults.[3-6] Although not all adult childhood cancer survivors appear to suffer from the late sequelae of their disease and/or treatment, many survivors do seem to experience problems, and often their tolerance of disability appears to decline with time. With the increasing number of long-term childhood cancer survivors, the need to improve their overall well-being or health-related quality of life (HRQoL) is becoming even more important and meaningful. 'Health-related quality of life' is seen as a multidimensional psychological construct, which includes at least four domains: physical, cognitive, social and emotional functioning.[7] In some recent studies of young adult survivors of childhood cancer, only small differences, or no differences at all were found between the HRQoL of survivors and healthy controls or norm data.[8-10] In all of these studies, survivors of childhood cancer are still young and the mean time since diagnosis is less than 20 years. But less is known about the HRQoL of survivors diagnosed more than 20 years ago.

Patients' perception of their quality of life may change over time. For example, many cancer patients report benefits from their illness, ranging from an increased ability to appreciate each day, to greater feelings of personal strength, such as more satisfaction with their global quality of life than healthy comparison groups.[11-14] This paradox is considered to reflect a psychological adaptation that occurs in cancer patients as well as in patients with other chronic diseases.[15] It is possible that this mechanism will decline as time since diagnosis increases and adverse late affects appear. With advancing age there is more chance of additional major life events, developing a functional limitation or experiencing chronic disease, which may influence the quality of life. We expected that survivors diagnosed more than 20 years ago might have more serious late effects and subsequently experience their HRQoL as worse compared to survivors diagnosed more recently.

The main purpose of this study was to assess HRQoL of adult long term (up to 20 years) and very long term (>20 years) survivors of childhood cancer, compared to the HRQoL of a comparable group of the Dutch population. The second purpose was to grade treatment- and cancer-related late effects and their impact on the functional, psychological and social health of the childhood cancer survivors.

2. PATIENTS AND METHODS

The present study was performed at the Division of Paediatric Oncology of the University Medical Center in Groningen (UMCG), The Netherlands. Three hundred sixty three survivors were included in this study. The study population was composed of 227 childhood cancer survivors and patients with Langerhans cell histocytosis (LHC), ≥18 years, treated with chemo and/or radiotherapy, who had attended the long-term follow-up (LTFU) clinic since 1995. In addition an at-random sample of 136 survivors out of 336 eligible survivors who had been treated in the Department of Pediatric Oncology in the past, but were not yet involved in any kind of follow-up, were recalled to the LTFU clinic and included in this study.

Furthermore, eight bone tumour survivors (osteosarcoma or Ewing's sarcoma) who were older than 18 years at the time of diagnosis and whose chemotherapy at that time had been delivered by the paediatric oncologist were included as well. Brain tumour survivors were not included because they are followed at a separate clinic. All patients were seen by a doctor with special interest in late effects. According to their diagnosis and treatment in the past, the patients underwent risk-based evaluations such as hormonal assessments, echo-cardiography, bone mineral density tests or pulmonary function tests.

All late effects diagnosed by means of history, physical examination or testing were recorded in a database. Medical data on diagnosis, treatment and health problems were obtained from this registry of the local LTFU clinic. To determine the need for medical and psychosocial care, late effects were graded in terms of severity and the survivors' QoL was measured with the RAND-36. In order to compare the HRQoL between survivors with different lengths of follow-up, we divided the study population into a LF group (LTFU ≤20 years n = 129) and a VLF group (very LTFU, followup>20 years n = 184).

The cut-off point of 20 years was based on the fact that to our knowledge in the literature no HRQoL studies have been performed that included a significant number of survivors diagnosed more than 20 years ago.

2.1. Health-related quality of life (HRQoL)

We used the RAND-36[16] to assess HRQoL. The RAND-36 is an internationally used valid and reliable generic self-report questionnaire to assess HRQoL. It contains eight different subscales: physical functioning (PF), social functioning (SF), role limitations due to physical problems (RP), role limitations due to emotional problems (RE), mental health (MH), vitality (VT), bodily pain (BP) and general health perception (GH). For each subscale, scores were coded, summed up and transformed to a scale from 0 (worst health) to 100 (best health). The questionnaire takes about 10 min to complete. The instrument has been translated in Dutch[17] and has been validated for the Dutch population.[18] For the LF pa-

tients we used the mean scores of the available Dutch norm group, aged 18– 34 years (n = 356), and for the VLF patients the mean scores of the available Dutch norm group, aged 25–44 years (n = 416).

2.2. Grading of late effects

Late effects were graded using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3), developed by the National Cancer Institute (NCI). The NCI common toxicity criteria (CTCv1.0) was created in 1983 to aid in the recognition and grading of adverse effects of chemotherapy. It was updated and expanded in 1998 (CTCv2.0) but remained focused on acute effects.[19] The third version of the CTC has been renamed as common terminology criteria for adverse events v 3.0. The CTCAEv3 represents the first comprehensive, multimodality grading system to include both acute and late effects.[20]
The CTCAEv3 grades adverse effects from 0 to 4. Grade 1 effects are minimal and usually asymptomatic. Grade 2 effects are moderate, are usually symptomatic but do not impair activities of daily living. Grade 3 effects are considered severe requiring more serious interventions. Grade 4 effects are potentially life threatening. Low-grade events (Grades 1 and 2) are considered tolerable and manageable and should be distinguished from severe or very undesirable high-grade events (Grades 3 and 4).

2.3. Analysis

The statistical package for social sciences (SPSS) Windows version 11.0 was used for the statistical analyses. Descriptive statistics were calculated for all of the variables. Differences between the mean scores of the RAND-36 in the survivors groups and the Dutch standard population were tested with the One-Sample T-test. Differences in mean scores of the RAND-36 between LF-and VLF patients were analysed with the Student's t-test. Categorical variables were analysed using the Pearson Chi-Square test. Univariate relationships between demographic, medical and treatment issues on one hand, and RAND-36 scores on the other hand were assessed by Pearsons correlation coefficients. To investigate which variables predict the survivors QoL, all significant characteristics identified from univariate analysis were studied with multiple linear regression analysis. A significance level of $P < 0.05$ was applied in all the analyses.

3. RESULTS

The RAND-36 was sent to 363 survivors, who fulfilled the inclusion criteria and returned by 313 patients (response rate 86.2%). The characteristics of patients who returned the questionnaire were compared with the characteristics of those who did not. The respondents were older (median age 29, range 19–60) than the non-respondents (median

age 25, range 20–39) and the time since diagnosis in the respondents was longer (median duration 23 years, range 7–38) than that in the non-respondents (median duration 17.5 years, range 9– 34). No significant differences were found in gender, diagnosis, age at diagnosis and health problems as registered at the LTFU clinic.

The demographic and clinical data of the 313 included LF and VLF survivors are shown in Table 1. The survivors had been treated for a variety of cancers or LCH. The most frequent diagnoses were leukaemia, malignant lymphoma, bone tumour and Wilms' tumour. Due to the inclusion criteria, VLF patients were older and the time since diagnosis was longer. More VLF leukaemia patients had undergone cranial radiation (CR) (42.4%) than LF leukaemia patients (14.7%, $P < 0.001$) and they had received more often a combination of chemo-and radiotherapy (58.7% versus 34.9%, $P < 0.001$). VLF patients had significantly more severe late effects (47.8%) than LF patients (27.9%, $P < 0.001$) (Table 1).

Table 1 – Demographic and clinical data of 313 participating LF and VLF survivors

	LF group (n = 129)	VLF group (n = 184)
Patient characteristics		
Age at study[b]	24 (19–45)	32 (21–60)[a]
Age at diagnosis[b]	10 (0–27)	5 (0–38)[a]
Time since diagnosis[b]	16 (7–20)	26 (21–38)[a]
Male[c]	68 (52.7)	94 (51.1)
Type of cancer[c]		
Leukaemia	53 (41.1)	80 (43.5)
Malignant lymphoma	34 (26.4)	24 (13.0)
Bone tumour	12 (9.3)	26 (14.1)
Soft tissue sarcoma	7 (5.4)	16 (8.7)
Wilms' tumour	10 (7.8)	12 (6.5)
Langerhans cell histiocytosis	3 (2.3)	11(6.0)
Other	10 (7.8)	15 (8.2)
Treatment[c]		
Cranial radiation	19 (14.7)	78 (42.4)[a]
Chemotherapy only	70 (54.3)	65 (35.3)[a]
Radiotherapy only	6 (4.7)	7 (3.8)
Chemo-and radiotherapy	45 (34.9)	108 (58.7)[a]
Late effects[c]		
No late effect	45 (34.9)	16 (8.7)[a]
Mild late effect	48 (37.2)	80 (43.5)
Severe late effect	36 (27.9)	88 (47.8)[a]

a $P < 0.001$.
b Years, median (range).
c Number (%).

3.1. Quality of life (RAND-36)

The outcomes on the various subscales of the RAND-36 for the standard population, the LF patients, and the VLF patients are shown in Table 2.

Table 2 – Means and standard deviations for the RAND-36 subscales for LF patients, VLF patients and the Dutch comparison groups LF (18–34 years) and VLF (25–44 years)

	LF patients (n = 129)		VLF patients (n = 184)		Comparison group LF (n = 356)		Comparison group V LF (n = 416)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PF	90.6	14.1	85.6a	18.7	90.3	16.6	89.7	16.3
SF	85.2	22.8	83.0b	21.1	88.7	18.3	89.4	17.0
RP	86.4	27.8	78.6	33.8	83.8	31.2	82.7	32.2
RE	87.1	30.2	84.3	32.2	84.6	31.5	84.6	31.5
MH	77.0	16.9	75.9	15.3	76.8	18.7	77.9	17.7
VT	66.7	19.6	62.6b	19.6	69.1	18.8	68.2	18.9
BP	90.1b	16.9	82.8	19.8	85.5	22.8	84.0	22.9
GH	73.5	18.0	67.7b	22.6	77.4	20.0	75.9	20.2

LF: long term follow-up ≤20 years; VLF: very long-term follow-up >20 years; PF: physical functioning; SF: social functioning; RP: role limitations due to physical problems; RE: role limitations due to emotional problems; MH: mental health; VT: vitality; BP: bodily pain; GH: general health perceptions.
a $P < 0.01$: difference between survivors and comparison group.
b $P < 0.001$: difference between survivors and comparison group.

LF patients did not score significantly lower on the RAND-36 subscales compared to the standard population. On the subscale bodily pain, they even scored significantly better ($P < 0.01$). VLF survivors showed worse HRQoL scores in comparison to the standard population on the subscales physical functioning (PF, $P < 0.01$), social functioning (SF, $P < 0.001$), vitality (VT, $P < 0.001$) and general health perception (GH, $P < 0.001$).

Fig. 1 shows the differences on the various RAND dimensions between the LF and VLF patients in comparison with the age matched standard population.

Difference scores were calculated by subtracting mean outcomes of the standard population from the results of the LF and VLF patients. Negative difference scores indicate worse outcomes than in the standard population. Compared with LF patients, VLF patients scored significantly worse on the subscales PF ($P < 0.01$), RP ($P < 0.05$), VT ($P < 0.05$) BP ($P < 0.001$) and GH ($P < 0.05$).

In Fig. 2, the difference scores for the various RAND dimensions are shown for patients treated with chemotherapy only or a combination of chemotherapy with radiotherapy, in comparison with those of the Dutch norm population.

Patients treated with a combination of radio- and chemotherapy showed lower scores on different subscales of the RAND but this was only significant for the subscale general health perception compared to those treated with chemotherapy only.

Although leukaemia patients treated with cranial radiation (n = 85) had lower scores on the RAND-36, they did not differ significantly from those who did not receive cranial radiation (n = 48) (Fig. 3).

Except for the bone tumour patients who scored significantly lower on the subscale physical functioning (PF) (mean score PF 71.0 versus 87.4), no significant differences could be detected between the different diagnoses concerning the results in the different RAND subscales.

Table 3 shows the regression coefficient b of gender, age at diagnosis, time since diagnosis and late effects per organ system for six subscales of the RAND-36. In general, males appreciate their HRQoL better than females. The presence of orthopaedic, neurological and psychosocial late effects is negatively related with the subscale physical functioning of the RAND-36 ($P < 0.001$). Psycho-social late effects are also negatively related to the subscales social functioning ($P < 0.001$), mental health ($P < 0.001$), vitality ($P < 0.001$), bodily pain ($P < 0.05$) and general health perception ($P < 0.05$). Gastro-intestinal late effects are negatively related to the subscales physical functioning ($P < 0.05$), social functioning ($P < 0.001$), vitality ($P < 0.01$) and general health perception ($P < 0.05$). Orthopaedic and cosmetical late effects are negatively related to the subscale bodily pain ($P < 0.05$) (Table 3).

3.2. Grading of late effects

Significantly more patients in the VLF group had severe (grades 3 and 4) late effects (88/184, 47.8%) than in the LF group (36/129, 27.9%, $P < 0.001$) (Table 1). The survivors who had been treated with a combination of chemo- and radiotherapy had more severe late effects (74/153, 48.4%) than those who had received chemotherapy only (37/135, 27.4%, $P < 0.001$). Leukaemia patients treated with cranial radiation (CR) had more severe late effects (40/85, 47.1%) than those who did not receive CR (8/48, 16.7%, $P < 0.001$).

Bone tumour and soft tissue sarcoma patients had the highest incidence of severe late effects. The numbers of sequelae graded according to the CTCAEv3 represent cumulative data (survivors with multiple late effects).

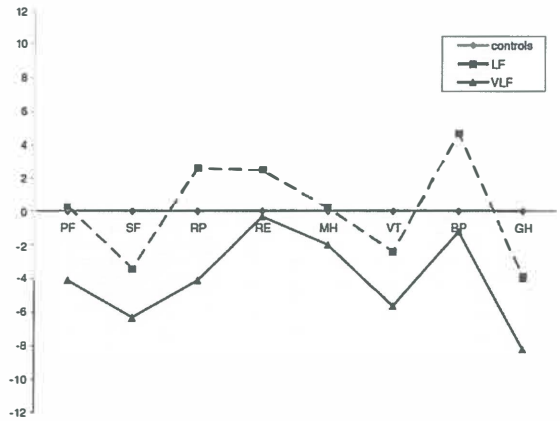

Figure 1. Difference in mean RAND scores of LF- (long-term follow-up, ≤20 years) and VLF patients (very long-term follow-up, >20 years) compared with an age matched Dutch standard population PF, etc. see Section 2.1.

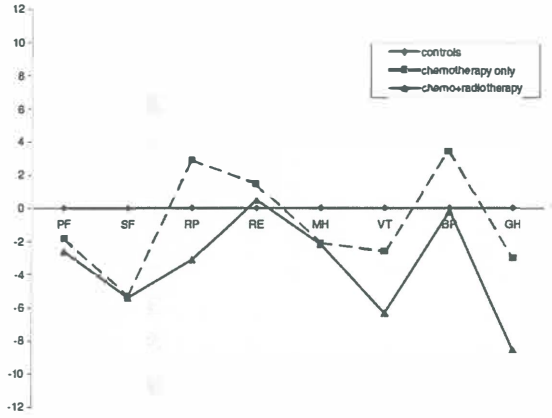

Figure 2. Difference in mean RAND scores of patients treated with chemotherapy and patients treated with a combination of chemo-and radiotherapy compared with a Dutch standard population PF, etc. see Section 2.1.

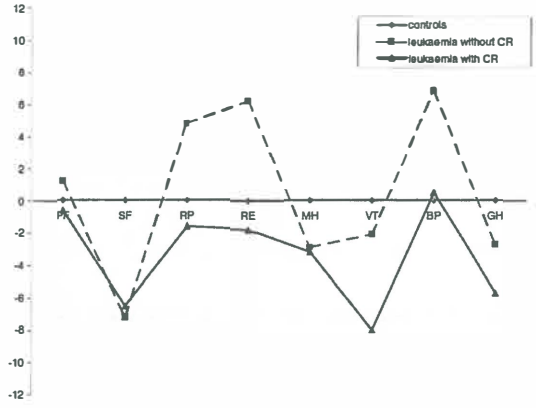

Figure 3. Difference in mean RAND scores of leukaemia patients treated with cranial radiation (CR) and leukaemia patients treated without CR compared with a Dutch standard population PF, etc. see Section 2.1.

Table 3: Regression coefficients b (95% confidence interval) of patient characteristics and late effects per organ system for six subscales of the RAND-36

variables*	PF	SF	MH	VT	BP	GH
gender(male)	6.6(3.4 to 9.9)	6.1(1.3- to 10.9)	3.2(-0.4- to 6.8)	9.0(4.8- to 13.2)	6.9(2.9to 11.1)	6.2(1.7 to 10.7)
age at diagnosis	-0.1(-4.5 to 0.2)	0.0(-0.5 to 0.5)	0.1(-0.3 to 0.5)	-0.5(-.09 to 0.4)	0.3(-0.1 to 0.7)	0.2(-0.2 to 0.7)
time since diagnosis	-0.2(-0.5 to 0.1)	-0,1(-0.5 to 0.3)	0.2(-0.2 to 0.5)	-0.4(-0.7 to 0.0)	-0.3(-0.65 to 0.8)	-0.2(-0.6 to 0.2)
late effects						
auditory	3.8(-3.1 to 10.7)	1.7(-8.6 to 11.9)	-1.8(-9.7 to 6.1)	0.0(-9.1 to 9.2)	6.3(-2.3 to 14.9)	4.1(-5.6 to 13.9)
cardiovascular	-11.7(-20.1 to -3.3)	-7.0(-19.5 to 5.5)	0.0(-9.4 to 9.4)	-2.2(-13.1 to 8.7)	-3.0(-13.5 to 7.5)	-9.3(-20.9 to 2.3)
cosmetic	-1.5(-5.7 to 2.7)	1.2(-5.1 to 7.5)	0.2(-4.6 to 4.9)	2.6(-2.9 to 8.1)	-6.8(-12.1 to -1.4)	-4.7(-10.6 to 1.2)
endocrine	3.0(-1.9 to 7.8)	2.8(-4.4 to 10.1)	0.6(-4.9 to 6.1)	2.9(-3.5 to 9.2)	-1.3(-7.4 to 4.9)	-0.5(-7.3 to 6.2)
gastroint.	-10.1(-19.3 to -0.8)	-16.6(-30.3 to -2.8)	-1.3(-11.7 to 9.0)	-17.9(-29.9 to -5.9)	-9.8(-21.8 to 2.2)	-16.2(-28.9 to -3.4)
neurology	-8.1(-12.7 to -3.5)	-0.6(-7.4 to 6.2)	-1.5(-6.7 to 3.6)	1.6(-4.4 to 7.6)	-5.1(-10.9 to 0.6)	-7.6(-13.9 to -1.2)
ocular/visual	-2.9(-11.1 to 5.4)	0.1(-12.1 to 12.4)	3.8(-5.4 to 13.0)	0.1(-10.6 to 10.8)	-0.4(-10.7 to 9.9)	-8.4(-19.8 to 3.0)
orthopaedic	-20.6(-25.9 to -15.3)	1.6(-6.3 to 9.5)	-0.4(-6.5 to 5.6)	2.3(-4.7 to 9.4)	-8.6(-15.5 to -1.8)	-8.8(-16.2 to -1.3)
psycho/social	-8.8(-13.4 to -4.1)	-15.6(-22.5 to -8.7)	-9.8(-15.0 to -4.6)	-11.5(-17.6 to -5.5)	-6.2(-12.0 to -0.4)	-6.4(-12.8 to 0.1)
pulmonary	-2.4(-8.9 to 4.2)	-7.3(-17.1 to 2.3)	-6.1(-4.6 to 4.9)	-10.3(-19.0 to -1.6)	-5.7(-13.9 to 2.5)	-6.4(-15.4 to 2.7)
renal/urinary	-2.2(-8.8 to 4.4)	-0.7(-10.6 to 9.1)	1.8(-5.7 to 9.2)	3.8(-4.7 to 12.5)	-1.3(-9.2 to 6.5)	5.1(-4.1 to 14.3)
sec. tumour	-1.6(-7.9 to 4.7)	-4.0(-13.4 to 5.4)	0.1(-6.9 to 7.1)	-6.1(-14.3 to 2.0)	-4.7(-13.1 to 3.8)	-1.6(-10.3 to 7.1)
reproductive	-2.8(-7.9 to 2.4)	2.8(-4.8 to 10.5)	1.0(-4.8 to 6.7)	2.7(-4.0 to 9.3)	-3.1(-9.6 to 3.3)	-7.5(-14.6 to -0.4)
Adjusted R Squared	0.32	0.08	0.02	0.13	0.14	0.14

* regression coefficient b, 95% confidence interval

4. DISCUSSION

Childhood cancer survivors with a follow-up of more than 20 years had significantly lower scores on the RAND-36 subscales physical functioning, vitality, bodily pain and general health perception and had significantly more severe late effects than those with follow-up less than 20 years. In agreement with other studies, the LF group showed only small differences in HRQoL compared with the Dutch standard group. Patients treated with a combination of chemo-and radiotherapy had significantly more late effects and lower HRQoL scores than those who were treated with chemotherapy alone. Female gender and late effects, especially psychosocial problems, were negatively related to HRQoL.

It has been stated that persons who have survived a life-threatening disease find their present life more satisfying as a result of psychological adaptation. This might occur in cancer patients as well as in patients with other chronic diseases.[8,14]

This could explain why LF patients score significantly better on the subscale bodily pain than the Dutch comparison group. It seems plausible that this mechanism may decline when time since diagnosis increases.

LF patients had different treatment protocols than VLF patients and the supportive care during treatment has improved over the years. The number of patients who received cranial radiation was higher in the VLF group, which might partly explain our finding that VLF patients have more severe late effects and lower scores on the RAND. But also if we exclude patients who received cranial radiation from the analyses, we still find significantly lower scores on various subscales of the RAND-36 in the VLF group compared with the LF group.

It seems likely that long-term effects in adults differ from those experienced in childhood or adolescence. New issues may come up, like worries about fertility, health of offspring and future health problems of their children. Negative consequences consistently reported in the literature concern job discrimination, difficulties in obtaining health and life insurance,[21,22] as well as lower rates of marriage and parenthood.[23] Also medical problems associated with aging may exhibit an earlier onset or more accelerated course following certain cancer therapies such as cardiovascular disease, osteoporosis or second malignancy.

Long-term follow-up of childhood cancer survivors is highly recommended by the American Cancer Society.[6] Regularly scheduled surveillance with early detection and treatment of late effects, combined with education concerning risk modification theoretically should have a positive impact on the quality of life and long term health of adult survivors.

From the literature, we know that the percentage of survivors involved in follow-up programmes decreases with age of the survivor. Adult survivors do not fit in paediatric clinics, and when they grow up, marry and change their name and/or address, they are

likely to be 'lost to follow-up'. In the CCSS analysis, only 31% of survivors who were 18–19 years of age at the time of interview had seen a health care provider at a childhood cancer centre in the previous two years. This percentage steadily decreased with age to 17% of those who were 35 years or older.[24]

Our study shows that survivors diagnosed more than 20 years ago have a higher percentage of severe late effects (47.8%) and perceive their QoL to be worse than survivors diagnosed more recently. In general, only a minority of VLF-survivors will attend a LTFU clinic. For these elder survivors it is important to establish new systems for follow-up, which are more flexible and appropriate to the needs of adult survivors.

Most survivors are in contact with a general practitioner (GP), but the average GP is not particularly aware of the risks of this population. GPs will increasingly come in contact with these patients, up to 8–9 in 2010.[25] Involving GPs in a shared care programme for long-term follow-up will increase their knowledge about the unique needs of childhood cancer survivors. It is important that GPs are well informed before their first interaction with a patient who is a childhood cancer survivor. Only then GPs will not miss the opportunities to recognise late effects and to intervene if possible. GPs are trained to promote good health practices and avoidance of risk-taking behaviours; this might help to decrease risky behaviour among cancer survivors. A Combined Model for long-term follow-up as described by Friedman,[26] in which long-term follow-up of childhood cancer survivors is a co-ordinated effort of the Cancer clinic and the patient's own GP, might be successful, but has not yet been studied.

Such a model could facilitate the necessary transition from paediatric-based care to adult care as childhood cancer survivors mature into adulthood. At the same time, GPs will become more prepared for the specific needs of the increasing number of adult survivors of childhood cancer.

Several limitations must be regarded in the interpretation of this study. Firstly, eight persons were older than 45 years, however, their exclusion did not change the outcome of this study.

Secondly, brain tumour survivors were not included in this study and there is an over-representation of leukaemia patients. Compared with leukaemia survivors, survivors of brain tumours are more likely to report adverse health.[27] In addition the instrument used was the RAND-36, which is a generic outcome measure focusing on health-related quality of life. To investigate the functioning of survivors more thoroughly, more specific questionnaires are needed. There are also other important aspects of the functioning of survivors as educational achievement, employment, marital status, additionally experienced life events and comorbidities, which we left out of the current study.

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CHAPTER 3

Late effects in adult survivors of childhood cancer: the need for life-long follow-up

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ABSTRACT

Background: To assess health status and health-related quality of life (HRQoL) in childhood cancer survivors who were not involved in regular long-term follow-up.

Patients and methods: One hundred and twenty-three long-term survivors, median age 33 (19–50) years, follow-up 27 (9–38) years, were recalled to the long-term follow-up clinic. Most of them were treated in the period 1970–1990. Late effects were graded using the Common Terminology Criteria for Adverse Events, version 3 (CTCAEv3). HRQoL was assessed by RAND-36. Socio-economic factors were compared with data from Statistics Netherlands (CBS).

Results: Grade 1–2 late effects were found in 54% of the survivors, grade 3–4 in 39%, two or more late effects in 70% and grade 2–4 previously unknown late effects in 33%. Survivors had significantly lower scores on RAND-36 compared with controls.

Conclusions: As nearly 40% of these long-term childhood cancer survivors suffer from moderate to severe late effects and 33% had previously unknown late effects it is worthwhile recalling these patients to follow-up. Where and by whom this follow-up can best be done is still a question that needs to be answered.

Key words: childhood cancer survivors, grading of late effects, long-term follow-up, HRQoL

INTRODUCTION

As a result of improved survival of childhood cancer there is a growing population of long-term survivors.[1] This ever enlarging population of young adult childhood cancer survivors is at increased risk of considerable morbidity and even mortality as a result of late adverse effects of their previous treatment.

Adverse late effects secondary to previous treatment with chemotherapy or radiation are common; as many as two-thirds of survivors of childhood cancer will experience such late effects.[2-5] All organ systems are at risk, with late effects including cognitive impairment, infertility, alterations in growth and development, organ system damage and second malignancies.[6,7] To ensure that survivors enjoy the best possible quantity and quality of life it is important to recognize and treat adverse effects if possible at an early stage.[7] Most clinicians advocate that childhood cancer survivors should be followed for life.[8,9] However, at present not all long-term survivors participate in long-term follow-up.

Many were discharged years ago and some doctors still discharge survivors as soon as they reach adulthood. From an analysis performed by the Children's Cancer Survivors Study Group (CCSS) it appeared that only 31% of survivors who were 18–19 years of age at time of interview had been seen by a health-care provider at a paediatric cancer centre in the previous 2 years. This percentage steadily decreased with age of the survivor, to 17% of those who were 35 years or older.[10] These older survivors reach a period in life when many common chronic diseases begin to arise. In addition, certain cancer treatments in childhood may cause an earlier or more accelerated course of these diseases, such as cardiovascular disease, osteoporosis or second malignancy.[11] Considering the risk of adverse late effects of treatment our hospital set up a long-term follow-up (LTFU) clinic in 1995. Childhood cancer survivors made a transition from the regular paediatric oncology clinic to this LTFU clinic as soon as they had been off-treatment for 5 years. From 2004 we recalled adult survivors who in the past, mostly in the period 1970–1990, had been discharged from the paediatric oncology clinic, which in those days usually occurred if they had no evidence of disease for 5–10 years. Assessment of these adult survivors for possible adverse effects of treatment was done by a general practitioner (GP) employed by the paediatric oncology department and trained by the paediatric oncologists. The objective of this manuscript is to report the health status and health related quality of life (HRQoL) of all survivors seen in the first year by the GP.

METHODS

patients

Patients were eligible for recall to the LTFU clinic if they had been treated previously at the paediatric oncology department of the University Medical Center Groningen, The Netherlands, were at least 5 years off-treatment and were not yet involved in any childhood cancer follow-up in either the same hospital or elsewhere. One hundred and thirty-three out of 210 eligible patients were chosen at random and recalled to the LTFU clinic between May 2004 and May 2005. Ten of them (8%) refused for several reasons, most often because they did not want to look back but wanted to look forward and rebuild their life. The remaining 123 patients (66 males, 57 females) were seen by a doctor with special interest in late effects. According to their diagnosis and treatment in the past, the patients underwent risk-based evaluations such as hormonal assessments, echocardiography, bone mineral density tests or pulmonary function tests. Due to the fact that Dutch guidelines are still under development, we followed the guidelines according to the practice statement 'Therapy Based Long Term Follow Up' produced by the United Kingdom Children's Cancer Study Group (UKCCSG) Late Effects Group (LEG). In addition patients who had received chest irradiation and therefore were at risk for coronary disease underwent electron beam computed tomography (EBCT), which is a non-invasive test to detect calcium deposits in the coronary arteries. Coronary artery calcification is expressed as a calcification score, the standard method is described by Agatston et al.[12] A total calcium score is determined by summing up the individual scores from each of the four coronary arteries. The scores are compared with the percentile ranks of Hoff et al.[13], which are adjusted for age and gender. Patients were diagnosed with childhood cancer between 1968 and 1997. Patients with a central nervous system tumour were excluded because most of them were followed separately by a multidisciplinary neuro-oncology team. No significant differences were found in gender, diagnosis and age at diagnosis between the study group and the 87 patients who were not yet recalled. Characteristics of the participating patients are shown in Table 1. Socio-economic factors of the study group were compared with an age-matched group in the Dutch population, analysed by Statistics Netherlands (CBS).

grading of late effects

Late effects were graded using the Common Terminology Criteria for Adverse Events, Version 3 (CTCAEv3), developed by the National Cancer Institute (NCI). The CTCAEv3 represents the first comprehensive, multimodality grading system to include both acute and late effects.[14] The CTCAEv3 grades adverse effects from 0 to 4. Grade 1 effects are minimal and usually asymptomatic. Grade 2 effects are moderate, are usually symptomatic but do

not impair activities of daily living. Grade 3 effects are considered severe, requiring more serious interventions. Grade 4 effects are potentially life threatening. Low-grade events (grades 1 and 2) are considered tolerable and manageable and should be distinguished from severe or very undesirable high-grade events (grade 3 and 4).

health related quality of life

HRQoL was assessed by RAND-36, which is an internationally used valid and reliable generic self-report questionnaire. It contains eight different subscales: Physical Functioning (PF), Social Functioning (SF), Role limitations due to Physical problems (RP), Role limitations due to Emotional problems (RE), Mental Health (MH), Vitality (VT), Bodily Pain (BP) and General Health perception (GH). For each subscale, scores were coded, summed up and transformed to a scale from 0 (worst health) to 100 (best health).[15] The questionnaire takes about 10 min to complete. The instrument has been translated into Dutch[16] and has been validated for the Dutch population.[17] RAND-36 has already been used in several other studies for assessment of HRQoL in childhood cancer survivors.[18,19] Mean scores of the available Dutch norm group aged 25–44 years (n = 416) were used as reference values.

Table 1. Demographic and clinical data of 123 participating adult survivors

	Study group (n = 123)	CBS
Patient characteristics		
Age at study (years)[a]	33 (19–50)	
Age at diagnosis (years)[a]	6 (0–20)	
Time since diagnosis[a]	27 (9–38)	
Male[b]	66 (53.7)	
Living with parents[b]	24 (19.5)	9%
Living with a partner[b]	70 (56.9)	
Childless[b]	74 (60.2)*	50%
Type of cancer[b]		
Leukaemia	56 (45.5)	
Malignant lymphoma	21 (17.1)	
Bone tumour	19 (15.4)	
Soft tissue sarcoma	7 (5.7)	
Wilms' tumour	4 (3.3)	
Langerhans cell histiocytosis	8 (6.5)	
Other	8 (6.5)	
Treatment[b]		
Chemotherapy only	45 (36.6)	
Radiotherapy only	5 (4.1)	
Chemo- and radiotherapy	71 (57.7)	
Cranial radiation	55 (44.7)	
Surgery only	2 (1.6)	

[a]Median (range). [b]Number (%).
*$P < 0.05$.
CBS, Statistics Netherlands.

statistics

Data were analysed by descriptive techniques using frequencies, percentages, means and medians as appropriate. The one-sample t-test was used to compare the mean RAND scores of the study group with the mean scores of the Dutch control group. The one-sample t-test was also used to compare socio-economic variables of the study group with an age-matched control group from the Dutch population. Because of the small study population, differences between cancer types were not analysed. To investigate which variables predict survivors QoL, all significant characteristics identified from univariate analysis were studied with multiple linear regression analysis. A significance level of $P < 0.05$ was applied in all analyses.

RESULTS

Sixty-six out of 123 (54%) patients had a mild late effect (grade 1 or 2) and 48/123 (39%) had a moderate to severe late effect (grade 3 or 4) (Table 2). Almost 70% had two or more late effects. Forty-one out of 123 patients (33%) were diagnosed with a grade 2–4 late effect that was previously unknown and that required treatment or closer surveillance (Table 3).

Table 2. Late effects graded with Common Terminology Criteria for Adverse Events (CTCAE) version 3 in 123 survivors

Category	n	%
No late effect	9	7
Grade 1 or 2	66	54
Grade 3 or 4	48	39
Single late effect	29	24
Two or more late effects	85	69

Table 3. Previously undetected late effects that required therapy or closer surveillance in 123 survivors

Category	n	%
Second malignancy	5	4
Growth hormone deficiency	8	6
Osteoporosis	7	6
Arthrosis hip (osteonecrosis)	2	2
Cardiac problem	10	8
Reproductive problem	7	5
Hepatitis C	1	1
Thyroid problem	1	1
Total	41	33

Five survivors had a second malignant tumour (meningioma, oesophageal carcinoma and three basocellular carcinomas) that had not been recognized before and eight patients had a previously unknown growth hormone deficiency. Seven patients, four with Hodgkin's lymphoma, two with non-Hodgkin's lymphoma and one with a rhabdomyosarcoma, who had been treated with chest radiation, underwent electron beam tomography because they were at risk for coronary artery disease. All of them had Agatston scores >90th percentile ranks of Hoff et al. [13] and three (43%) had Agatston scores >400. These patients were referred to the cardiologist for further cardiac evaluation (Table 3). Patients treated with a combination of chemo- and radiotherapy had significantly ($P < 0.001$) more moderate to severe late effects compared with patients treated with chemotherapy alone. Survivors lived significantly more often with their parents than an age-matched group from the Dutch population (19.5% vs. 9%, $P = 0.004$) and were more often childless (60.2% vs. 50%, $P = 0.024$) (Table 1). The RAND-36 was sent to all 123 participating survivors before they visited the LTFU clinic, and was returned by 121 (98%) of them. The outcomes on the various subscales of the RAND-36 for the study group and the Dutch control group are shown in Table 4. Survivors showed lower HRQoL scores in comparison to the control group on the subscales PF ($P = 0.033$), SF ($P = 0.009$), VT ($P = 0.003$) and GH ($P = 0.000$). Survivors who had no late effects, or only mild late effects, had significantly better scores on the RAND subscales PF ($P = 0.023$, $P = 0.011$), RP ($P = 0.030$, $P = 0.044$), VT ($P = 0.009$) and GH ($P = 0.003$) than survivors who had severe late effects. Survivors with a job had significant better scores on the RAND subscales PF ($P = 0.019$) and GH($P = 0.017$). Living

Table 4. Means and standard deviations for the RAND-36 subscales, in 123 survivors and in Dutch controls (25-44 years)

	Study Group (n = 123)		Controls (n = 416)	
	Mean	SD	Mean	SD
PF	**85.9**[a]	19.2	89.7	16.3
SF	**84.7**[a]	19.5	89.4	17.0
RP	79.5	32.5	82.7	32.2
RE	87.5	28.7	84.6	31.5
MH	77.2	15.9	77.9	17.7
VT	**62.7**[a]	20.1	68.2	18.9
BP	83.8	19.5	84.0	22.9
GH	**67.2**[b]	22.6	75.9	20.2

[a] $p < 0.01$: survivors versus controls
[b] $p < 0.001$: survivors versus controls
PF: physical functioning; SF: social functioning; RP: role limitations due to physical problems; RE: role limitations due to emotional problems; MH: mental health; VT: vitality; BP: bodily pain; GH: general health perceptions.

with a partner was related to higher scores on the subscales RE (P = 0.027) and MH (P = 0.003). Patients who received cranial radiation had unexpectedly significantly better scores on the RAND subscales GH and BP compared with those who had not received cranial radiation.

DISCUSSION

This study shows that a substantial number (39%) of survivors who were treated in the period 1970–1990 have moderate to severe late effects with significantly lower quality of life as expressed by scores on the RAND-36 and compared with survivors who have no or only mild late effects. Thirty-three per cent of these late effects were previously unknown and required treatment or closer surveillance. Some of these late effects, such as a meningioma, were diagnosed following specific complaints and symptoms that were reported at the long-term follow-up clinic and that had failed to be appreciated until then. This suggests that education of patients as well as physicians who might be involved in follow-up care of these survivors is an important issue. Our results support the importance of life-long follow-up by physicians with knowledge of late effects. In addition more strategies have to be developed to improve the knowledge of childhood cancer survivors and non-specialist clinicians, such as for example the UKCCSG's 'After cure package'. Research will continue to have an important role in LTFU to develop reduced treatment strategies for treatment of the primary disease, like reduced doses of radiation and chemotherapy, less toxic chemotherapy and addition of cardioprotectants, which can maintain high cure rates with less late toxicity. Detection and treatment of problems that would otherwise be neglected or detected much later may improve patients' future quality of life. The data from the current study confirm the findings of other studies that a significant proportion of childhood cancer survivors have moderate to severe late effects that require treatment, and affect their HRQoL .[2,20] However, the percentages in our study are even higher than those found by others who found approximately 30% patients with moderate to severe late effects (versus 39% in our study) and approximately 40% with two or more late effects (versus 70% in ours).[2-4,20] Most research has focused on the late effects during the first 10–15 years after therapy. In our study time since diagnosis was longer than 20 years, which is longer than in most other studies. In an earlier study we showed that the prevalence and the severity of late effects increased with time since diagnosis.[21] As time since diagnosis extends, medical problems associated with aging may exhibit an earlier onset or more accelerated course following certain cancer therapies. Oeffinger[11] described that cancer survivors, diagnosed with cancer between 1970 and 1986, were more vulnerable to diseases that are associated with aging, like second cancers, heart conditions, kidney disease, musculoskeletal problems, osteoporosis and sterility compared with their

siblings. The incidence of chronic conditions increases over time and does not appear to plateau. Survivors lived significantly more often with their parents and were more often childless than an age-matched group from the Dutch population. Other studies confirm these findings and they also find that a lower percentage of survivors than peers are in employment [22,23], which we did not include in our study. In our study, survivors who did not have a partner had a lower quality of life, expressed as lower scores on the physical functioning and general health perception subscales of the RAND-36 and those without a job had lower scores on the role limitations due to emotional problems and mental health subscales. This might be explained by the fact that these survivors lack emotional support from a partner and are likely to have lower incomes. In the CCSS studies survivors with low household income were at risk for adverse health status.[23] Several limitations can be recognized in the interpretation of the current study. The sample size was relatively small, limiting analysis between cancer types or different treatment modalities. Patients with CNS tumours were not included. This might have caused an underestimation of late effects and an overestimation of HRQoL, as these survivors generally exhibit more severe treatment sequelae.[19,23,24] Quality of life was measured by RAND-36, which is a generic outcome measure focusing on HRQoL. RAND-36 has been used in several other studies to determine HRQoL in adult childhood cancer survivors.[18,19] Specific questionnaires would probably be better to measure the functioning of survivors, but validated questionnaires designed for childhood cancer survivors in particular are hardly available. Finally, some patients, especially those with cognitive defects following cranial irradiation, were not able to complete the RAND-36 correctly and needed help from family members. This might have influenced the outcome. One could speculate that family members are probably positively biased with regard to their kin's quality of life. Apparently the RAND-36, as a self-report questionnaire, is less suitable for patients with impaired cognitive functions. This could be an explanation for our finding that survivors treated with cranial radiation had higher scores on the subscales bodily pain and general health perception. This study supports the fact that the growing population of aging childhood cancer survivors can be viewed as a high-risk population for an impaired health status and HRQoL, and supports the necessity of life-long follow-up.

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CHAPTER 4

Knowledge of disease and treatment in adult survivors of childhood cancer

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ABSTRACT

Objective: If childhood cancer survivors are aware of potential late effects of treatment they are more likely to seek appropriate medical assistance if health problems occur. Therefore we assessed knowledge of disease, treatment and potential late effects in adult survivors.

Methods: Between 2004 and 2006 all adult survivors attending appointments at the long-term follow-up clinic (LTFU) were asked to complete a ten-item questionnaire on knowledge of disease, treatment and late effects.
Survivors were divided into recalled survivors (survivors who were discharged before 1995 and recalled in follow-up care) and regular survivors (survivors who were attending regular appointments). Total knowledge score (TKS) was calculated as a percentage of the maximum possible number of correct answers.

Results: Questionnaires were completed by 95.4% (186 out of 195) of the survivors; 89.8% (167 out of 186) knew the name of the cancer, and 57.5% (107 out of 186) knew the precise diagnosis. Of those who knew that they had received radiotherapy, 71.9% (77 out of 107) knew the radiation field; of those who knew that they had undergone surgery, 75.0% (60 out of 80) knew the details of the procedure; and of those who had chemotherapy only two knew the chemotherapeutic agents. The TKS score in Group regular was higher than in Group recalled (83.3% vs. 71.4%; $p = 0.026$). Group regular survivors were more aware of potential late effects than Group recalled survivors ($p = 0.004$). TKS was positively correlated with being aware of potential late effects ($p < 0.0005$).

Conclusion: Although nearly 90% of the survivors knew the rough name of the cancer there are still some noteworthy knowledge deficits. Survivors who were recalled in follow-up had lower TKS and were less aware of potential late effects than those who had regular appointments.

Practice Implications: It is worthwhile to recall adult survivors who were discharged in an earlier period to follow-up, not only for the purpose of screening, but also to improve their knowledge of cancer diagnosis and treatment.

Keywords: childhood cancer survivors, knowledge of disease, survivorship care plan.

INTRODUCTION

The treatment of childhood cancer is a success story. Since the 1970s, cure rates have increased to more than 75 percent.[1] This increase in survival rates for childhood cancer is reflected in a growing population of young adult survivors. At the same time, it has become clear that the success of cure has its price. The adverse late effects of the treatment for childhood cancer may present themselves after many years, sometimes well after these children reach adulthood. The most common late effects of childhood cancer and its treatment are neurocognitive defects, as well as psychological, cardiopulmonary, endocrine and musculoskeletal late effects .[2] Moreover, there is an increased risk of second malignancies. It has been estimated that approximately two-thirds of adults who survive childhood cancer have at least one late complication and approximately one-third have serious or life-threatening complications.[2-5] Recognition of these serious late effects has led to the recommendation of lifelong follow-up of these survivors. Many paediatric oncology centres have started dedicated long-term follow-up clinics (LTFU) for the monitoring of childhood cancer survivors, of whom many are now adults.

There is general agreement that a follow-up programme for cancer survivors should have two fundamental aims: to provide clinical care and to conduct research.[6] Another purpose of long-term follow-up is to improve survivors' knowledge of their diagnosis and treatment and to increase their awareness of potential late effects. Adequate knowledge might encourage survivors to participate in follow-up programmes. Moreover, they will be better equipped to provide appropriate information to health care providers. Results of earlier studies have shown significant knowledge deficits among adult survivors of childhood cancer regarding their disease and treatment.[7-9] At the Paediatric Oncology Department of the University Medical Center Groningen (UMCG), in the Netherlands, a LTFU clinic was established in 1995. Since then childhood cancer survivors have been followed at regular intervals by a paediatric oncologist with a special interest in late effects. Recently we started recalling survivors who had been discharged in the pre-1995 era. On their first visit to the LTFU clinic all survivors or their parents receive an information booklet developed by the Dutch Childhood Cancer Parent Organization. This booklet provides a brief explanation of the rationale for follow-up and recommendations for healthy behaviour. In addition, everyone receives personalized information about their cancer diagnosis, its treatment and the potential late effects.

The aim of our study was to assess the knowledge of adult survivors of childhood cancer with respect to disease, details of the treatment and risk of late effects. We compared the knowledge of survivors who were discharged before 1995 and now recalled for the first time for follow-up (*recalled* survivors) with the knowledge of survivors who were attending regular appointments (*regular* survivors).

PATIENTS AND METHODS

Patients

All survivors aged 18 years and older, who attended the LTFU clinic between September 2004 and September 2006, were included. In this cohort there were no brain tumour survivors because these patients attend a separate neuro-oncology follow-up clinic. Survivors were divided into two groups. *Recalled* survivors consisted of survivors who were discharged from the clinic before 1995 and were now recalled to the LTFU-clinic for the first time. *Regular* survivors consisted of survivors who were attending regular appointments at the LTFU-clinic. As a rule all survivors or their parents receive an information booklet at the first consultation at the LTFU clinic. This booklet, which is developed by the Dutch Childhood Cancer Parent Organisation, provides brief information about the rationale for follow-up of childhood cancer survivors and recommendations for healthy behaviour. In addition personalised information about the cancer diagnosis of the patient, its treatment and potential late effects is provided. Consequently, recalled childhood cancer survivors participated in the current study prior to the delivery of the information booklet. Characteristics of the participating childhood cancer survivors are shown in Table 1.

Table 1: Patient characteristics

Patient characteristics	Entire group N=186	Recalled N=105	Regular N=81	P
Age at Diagnosis*	7 (0-17)	6 (0-17)	8 (0-16)	0.18
Age at Study*	29 (18-49)	33 (18-49)	24 (18-35)	< 0.0005
Follow-up*	23 (7-37)	26 (7-37)	17 (7-29)	< 0.0005
Male (%)	97 (52.2%)	57 (54.3%)	40 (49.4%)	0.51
Leukaemia	91 (48.9%)	53 (50.5%)	38 (46.9%)	0.65
Bone tumour	18 (9.7%)	12 (11.4%)	6 (7.4%)	0.45
Malignant Lymphoma	37 (19.9%)	20 (19.0%)	17 (21.0%)	0.85
Soft Tissue Sarcoma	13 (7.0%)	8 (7.6%)	5 (6.2%)	0.78
Wilms' tumour	14 (7.5%)	4 (3.8%)	10 (12.3%)	0.05
Other	13 (7.0%)	8 (7.6%)	5 (6.2%)	0.78
Chemotherapy	178 (95.7%)	98 (93.3%)	80 (98.8%)	0.14
Radiation therapy	109(58.6%)	68 (64.8%)	41 (50.6%)	0.07
Surgery	81 (43.5%)	44 (41.9%)	37 (45.7%)	0.65

* median, years (range)

Methods

In the waiting room prior to their appointment, all survivors were asked to complete a ten-item questionnaire. This questionnaire was based on the questionnaire used by Bashore et al.[7], which was validated by three cancer survivors and their parents as to the content of the questions, and consisted of eight questions regarding knowledge of disease and treatment, and two additional questions (Table 2).

Table 2 Questionnaire on knowledge about diagnosis, treatment, late effects and summary

Questionnaire: correct answers in numbers (%)		Total (n=186)	Group N (n=105)	Group R (n=81)	P
1. What is the name of the disease?		167 (89.8)	91 (86.7)	76 (93.8)	0.144
2. What is the specific diagnosis?		107(57.5)	55 (52.4)	52 (64.2)	0.135
3. Did you receive chemotherapy?					
Received chemotherapy (n=178)		169(96.0)	90 (91.8)	79 (98.8)	0.043
Received no chemotherapy(n=8)		7 (87.5)	6 (85.7)	1 (100.0)	1.000
4. Can you recall the names of the cytostatic agents?	correct	2 (1.2)	1 (1.1)	1 (1.3)	0.509
	partially correct	36 (21.3)	16 (17.8)	20 (25.3)	
	incorrect	131 (77.5)	73 (81.1)	58 (73.4)	
5. Did you receive radiotherapy?					
Received radiotherapy (n=109)		107(98.2)	66 (97.1)	41(100.0)	0.526
Received no radiotherapy (n=77)		67 (87.0)	32 (86.5)	35 (87.5)	1.000
6. Do you know the radiation field?	correct	77 (71.9)	44 (66.7)	33 (80.5)	0.239
	partially correct	14 (13.1)	11 (16.7)	3 (7.3)	
	incorrect	16 (15.0)	11 (16.7)	5 (12.2)	
7. Did you undergo surgery?					
Received surgery (n=81)		80 (98.8)	44(100.0)	36 (97.3)	0.457
Received no surgery (n=105)		101(96.2)	59 (96.7)	42 (95.5)	1.000
8. Can you tell us what kind of surgery was performed?	correct	60 (75.0)	31 (70.5)	29 (80.6)	0.355
	partially correct	8 (10.0)	4 (9.1)	4 (11.1)	
	incorrect	12 (15.0)	9 (20.5)	3 (8.3)	
9. Do you think late effects due to the former therapy may occur in the future?(n=177)		126 (71.2)	64 (62.7)	62 (82.7)	0.004
10. Did you receive a treatment summary? Yes				33 (40.7)	
Percentage of Total Knowledge Score	median	75.0	71.4	83.3	0.026
	range	14.3-100	14.3-100	42.9-100	

If any of the treatment questions (Questions 3, 5 and 7) were answered positively, survivors were asked to list the chemotherapeutic agents, radiation fields and/or surgical procedures (Questions 4, 6 and 8). If survivors were able to list some of the chemotherapeutic agents or partly describe the radiation field or surgical procedure their answers were seen as partially

correct. Answers given to the first question – 'What was the name of the disease?' – such as leukaemia, renal tumour or bone tumour, for example, were seen as correct. However, a correct answer to the second question – 'What was the more specific diagnosis?' – had to be more precise, such as acute lymphatic leukaemia, Wilms' tumour, or osteosarcoma. The two additional questions were 'Do you think adverse late effects of therapy may occur in the future?' and 'Did you receive a treatment summary?' The latter question was only for regular survivors, who had all received a treatment summary on their first visit to the LTFU clinic.

For each participant, a TKS was calculated as a percentage of the possible maximum score of correct answers. If a person was treated with surgery as well as chemotherapy and radiotherapy, he/she was asked to answer all eight knowledge questions. However, if a person only received chemotherapy, only six knowledge questions were asked, as the questions about surgical procedures (Question 8) and the radiation fields (Question 6) were not relevant. The answers of the participants were compared with information from their medical records.

Statistical analysis

Descriptive statistics were used for all variables. Chi-square, Mann-Whitney and Fisher's Exact Test were used to compare patient characteristics and results of the questionnaire between recalled survivors and regular survivors. In a multiple linear regression model the TKS was correlated with group, gender, age at diagnosis, time since diagnosis, radiotherapy, chemotherapy, surgery, having received an information booklet and being aware of future health problems due to former treatment (Table 3). A significance level of $p<0.05$ (two-sided) was applied in all analyses.

Role of the funding source

The study was financially supported by the UMC Groningen, The Netherlands.

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. WT had access to the raw data.

Table 3: Linear regression model; variable Total Knowledge Score (percentage of correct answers)
Adjusted R square 0.157

	Unstandardized regression coefficients		p-value	95% Confidence Interval for b	
	b	Std. Error		Lower Bound	Upper Bound
(Constant)	71.84	15.22	<0.0005	41.79	101.88
Patientgroup	1.11	3.13	0.724	-5.07	7.28
Gender	2.66	2.23	0.234	-1.74	7.06
Expectations of future health problems due to former therapy	11.06	2.55	**<0.0005**	6.02	16.09
Treatment summary	3.28	2.93	0.265	-2.51	9.07
Surgery	0.16	2.44	0.948	-4.67	4.99
Radiotherapy	-1.25	2.31	0.591	-5.82	3.32
Chemotherapy	-13.00	5.77	**0.026**	-24.40	-1.60
Age at diagnosis	0.48	0.28	0.083	-0.063	1.03
Time since diagnosis	-0.08	0.25	0.755	-0.57	0.41

RESULTS

Of the 195 adult childhood cancer survivors who visited the LTFU clinic between September 2004 and September 2006, 186 (95%) completed the questionnaire. Eight survivors could not complete the questionnaire without help and were excluded from the analysis; one survivor refused to complete the questionnaire.
Median age at diagnosis was 7 years (0-17), median age at study 29 years (18-49) ; median follow-up was 23 years (7-37) . Common diagnoses were leukaemia (91 out of 186, 49%) and malignant lymphoma (37 out of 186, 20%) (Table 1). The number of *recalled* survivors was 105 (56%) and of *regular* survivors 81 (44%). *Regular* survivors were significantly younger at the time of the study compared with *recalled* survivors and time since diagnosis was significantly shorter.

Knowledge of diagnosis

Almost ninety percent (167/186) of the survivors knew the rough name of the disease, but only 107/186 (58%) knew the precise diagnosis. Not knowing the precise diagnosis

was significantly related to younger age at diagnosis (p=0.001) and longer time since diagnosis (p=0.012). Survivors who had undergone surgery knew the precise diagnosis more often (p=0.001) (Table 2).

Knowledge of diagnosis was not different between *recalled* and *regular* survivors.

Chemotherapy

Ninety- four percent (169/178) of the survivors who received chemotherapy answered correctly on the question "Did you receive chemotherapy". Five chemotherapy-treated patients thought that they had not received chemotherapy and four patients did not know whether or not they received chemotherapy. One of those who did not receive chemotherapy incorrectly thought he had. The answers of *regular* survivors were significantly more often correct than of recalled survivors (p=0.045). Being treated with surgery was positively related to correct answers to this question (p=0.045) (Table 1).

Only two of those who answered correctly when asked if they had received chemotherapy could list all of the chemotherapeutic agents. Thirty-six out of 169 (21%) of the survivors could mention one or two agents of a combination chemotherapy regimen; these answers were considered partially correct.

Radiotherapy

Ninety-eight percent (107/109) of the survivors who received radiotherapy answered correctly to the question "Did you receive radiotherapy". Two patients did not know whether they had received radiotherapy or not. Eighty-seven percent (67/77) of the survivors who did not receive radiotherapy knew this correctly, three patients thought incorrectly that they had received radiotherapy and seven patients did not know whether they had received radiotherapy or not. Older age at diagnosis (p=0.027) and female gender (p=0.025) were positively related to a correct answer on this question. Of those who answered correctly that they received radiotherapy, 72 % (77/107) were aware of the radiation field (Table 2). No differences were found between *recalled* and *regular* survivors.

Surgery

Nearly 99% (80/81) of the survivors who underwent surgery answered correctly to the question "Did you undergo surgery". Of the survivors who did not undergo surgery 96 % (101/105) knew this correctly. Four patients incorrectly thought that they had undergone surgery. Of those who answered correctly when asked if they had undergone surgery 75% (60/80) were aware of the surgical procedure (Table 2).

No differences were found between *recalled* and *regular* survivors.

Additional questions

Seventy-one percent (126/177) of the survivors answered yes to the question 'Do you think that late effects may occur in the future?' There was a significant difference between *recalled* survivors (64/102, 63%) and *regular* survivors (62/75, (83%); p=0.004) (Table 2).

Although all *regular* survivors had been handed a treatment summary on their first visit to the LTFU clinic, only 41% (33/81) could remember that they had received it.
Recalled survivors had a lower TKS than *regular* survivors (median score 71.4% (range 14.3-100) vs 83.3 (range 42.9-100) ; p=0.026) (Table 2). In the multiple linear regression model (Table 3) TKS was positively associated with being aware of future health problems that might arise due to the former treatment (p<0.0005). Survivors who underwent chemotherapy had a significantly lower TKS (p=0.026), although there is a very wide confidence interval (Table 3).

DISCUSSION

Although nearly 90% of the childhood cancer survivors knew the rough name of the cancer there were still some noteworthy knowledge deficits. In studies of the CCSS group[8] and of Bashore[7] similar percentages of survivors knowing the rough diagnosis were found (91% and 84%). In our study only 58% knew the precise diagnosis; this was lower than in the CCSS study (72%). This can be explained by the fact that in the CCSS study survivors were prompted with choices of names of different diagnoses. Knowledge, expressed as TKS, of survivors who were discharged from the clinic before 1995 and who were recalled to the LTFU-clinic was lower than that of survivors who had regular appointments at the LTFU clinic. Not knowing the precise diagnosis was significantly related to younger age at diagnosis and longer time since diagnosis. Lack of knowledge of disease and treatment is not only found in childhood cancer survivors but is also found in adults with congenital heart disease.[10]
In the past health care professionals and parents used to give only limited information to childhood cancer patients on the grounds of preventing anxiety and stress.[11] Only in more recent years health care providers started to realize that it is important to inform survivors about their potential risk of adverse late effects, so that survivors can take preventive health measures which may decrease health risk. This might explain the significantly better knowledge of their diagnosis and greater awareness of being at risk of late effects in *regular* survivors compared with *recalled* survivors, who were treated in an earlier era. Another explanation could be the fact that *regular* survivors had received a written summary of their disease, treatment and risk of late effects. On the other hand the role of written information can easily be overestimated, as only 33 out of 81 survivors (41%) who received written information could remember it.
In our study only two survivors could list all the chemotherapeutic agents they had received. Most chemotherapy regimen consist of several cytostatic drugs, having names that are eccentric to the average patient. Survivors who received chemotherapy had lower TKS score compared to patients who did not receive chemotherapy, probably because the

latter did not have to answer the difficult question about the chemotherapeutic agents and thus had a higher chance for correct answers.

Of those who answered correctly that they had received radiotherapy, 72% were aware of the radiation field, a comparable percentage was found in the CCSS study[8] (70%). Of those who answered correctly that they had undergone surgery almost 75% survivors knew the surgical procedure. In contrast to chemotherapy, surgery and radiotherapy often leaves visible signs, like scars and pigmentation. This could explain the higher percentage of survivors knowing the surgical procedure and radiation field.

It was striking that survivors who were treated with surgery had better knowledge of their former diagnosis. Perhaps, it was again the visibility of the surgical scar that made them more aware of their medical history and encouraged them to ask questions.

In our study more survivors (71%) were aware of the risk of late effects than in the studies of Bashore and the CCSS group. In these studies 30% and 35% of survivors, respectively, were aware of potential late effects.[7,8] The difference between Bashore's study and ours might be explained by the fact that the participants in Bashore's study were younger than in ours (median age 16 vs 29 years). As the prevalence of late effects increases with time since diagnosis[12,13] more survivors in our study, being older, will have encountered late effects. Participants in the CCSS study had a median age comparable to that in our study but they included 82 patients with a CNS tumour. It has been shown that these survivors in particular are likely to have knowledge deficits,[8,9] as many have brain damage and cognitive defects.[14] Our study did not include CNS tumour survivors. In our study multiple linear regression showed that a higher TKS was positively related to more awareness of the risk of late effects, which was not found in the CCSS study.

Limitations

As mentioned above our study did not include survivors of CNS tumours. This could have upgraded the number of correct answers in our study, as brain tumour survivors in general have a high risk of cognitive defects.

All participants were survivors who were willing to participate in long-term follow-up, which could have produced a selection bias as these individuals probably were already aware of the possible late effects of treatment. However, as only very few survivors declined the invitation to the LTFU clinic the probability of selection bias is considered negligible.

Recommendations

Survivors who were discharged from the clinic before 1995 and who were recalled to the LTFU-clinic had lower TKS and were less aware of future health risks than survivors who had regular appointments at the LTFU clinic. If survivors are not aware of possible health risks due to their former cancer treatment, there is a risk that they will be delayed in seeking health care if they experience health problems. Also if they do seek help, they will not be able to provide appropriate information to health care providers. It is worthwhile

to recall adult survivors who were discharged in an earlier period to follow-up, not only for the purpose of screening, but also to improve their knowledge of cancer diagnosis and treatment.

Handing out a written summary of diagnosis and treatment at the first LTFU-clinic appointment is not sufficient because more than half of the survivors could not remember they had received one. Some survivors were still at a very young age at this first visit and then the information was handed out to the parents. It would be recommendable that every survivor, reaching adulthood, receives a survivorship care plan. The survivorship care plan is a document created by those primarily responsible for the cancer treatment, providing detailed information regarding the patient's cancer and treatment history, but also guidelines for future follow-up, gives advice about a healthy lifestyle and indicates by whom and in what setting follow-up care is provided. The purpose of the survivorship care plan is to serve as a communication vehicle between the survivors and their healthcare providers. These plans should not be static but change over time in response to the aging of the survivor or to new knowledge about late effects or monitoring recommendations. Electronic medical records will assist in the regular updating of this plan. Whether such a survivorship care plan will help to improve survivors knowledge needs further study.

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CHAPTER 5

The effect of exercise counselling with feedback from a pedometer on fatigue in adult survivors of childhood cancer: a pilot study

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ABSTRACT

Objective: The aim of this study was to evaluate the results of home- based exercise counselling with feedback from a pedometer on fatigue in adult survivors of childhood cancer.

Patients: Adult survivors of childhood cancer were recruited from the long-term follow-up clinic (LTFU) of the University Medical Centre Groningen (UMCG), the Netherlands. A score of 70 mm on a Visual Analogue Scale (VAS; scale 0-100mm) for fatigue was used as an inclusion criterion. Controls were recruited by the survivors among their healthy siblings or peers.

Methods: The counselor encouraged during 10 weeks survivors to change their lifestyle and enhance daily physical activity such as walking, cycling, housekeeping and gardening. As a feedback to their physical activity the daily number of steps of each survivor was measured by a pedometer and registered using an online step diary at the start of the programme and after 4 and 10 weeks. Fatigue was the primary outcome measure, assessed with the Checklist Individual Strength (CIS) at start (T0), 10 weeks (T10) and 36 weeks (T36). Thirty-three healthy age-matched control persons were asked to complete the CIS.

Results: Out of 486 cancer survivors, 453 were interested and were asked to complete the VAS to measure fatigue; 67 out of 254 respondents met the inclusion criteria, 21 refused, 46 were enrolled and 8 dropped out during the study. The mean scores on the CIS in the survivors at T0 was 81.42 (SD ± 20.14), at T10 62.62 (SD ± 20.68), which was a significant improvement ($p< 0.0005$). At T36, the end of the study, the mean CIS score was 63.67 (SD ± 23.12), this was a significant improvement compared with the mean CIS at the start ($p<0.0005$). There was no significant difference in the mean CIS scores of the controls during the follow-up period.

Conclusion: The stimulation of daily physical activity using exercise counselling and a pedometer over ten weeks leads to a significant decrease in fatigue in adult survivors of childhood cancer, and this improvement lasts for at least 36 weeks.

INTRODUCTION

Fatigue can be defined as the perception of an unusual or debilitating sense of whole body tiredness, different from the usual sense of tiredness experienced by healthy individuals.[1]

Fatigue is one of the late effects of (childhood) cancer that negatively affects quality of life. The prevalence is unclear and the aetiology is not well understood but probably multifactorial. Whatever the causes of fatigue in childhood cancer survivors are, those who experience fatigue need help.

A number of studies show different outcomes for the prevalence of fatigue in this particular population, varying from 5%-40%.[2-4] Other studies found no difference at all in fatigue between survivors and controls.[5,6] Fatigue and lack of energy are reported to be common in the general population[7,8] and both are major complaints presented to general practitioners.[9] Prevalence of fatigue in the general population ranges from 11%-45%[7]. The survivors in our study are young adults whose life goals include starting a family, a professional career, and the realization of financial security. Fatigue is reflected in decreased QoL, especially when sufferers become too weary to fulfil the social roles that make life meaningful.[2,10]

Different types of interventions to decrease fatigue have been developed: exercise training, education, attention-restoring activities and psychosocial techniques. In a randomised study, cognitive behaviour therapy showed a significant reduction of fatigue in severely fatigued disease-free cancer patients.[11] There apparently is a relation between (lack of) exercise, QoL and fatigue.[12] In the general population, inactivity doubles the risk of fatigue.[7] Exercise programmes have shown positive results in the treatment of fatigue in cancer survivors.[13,14] Dutch rehabilitation programmes for fatigued cancer survivors, such as 'Recovery & Balance', combine exercise with psychological support and have shown positive results.[15] However, there are barriers to participate in these structured exercise programs. Participants in these programs are mostly survivors of adult cancer with a mean age of around 50 years, and young adult survivors of childhood cancer seldom participate.[15] Structured exercise programmes are time- consuming and especially young people – who often have jobs and raise a family -, are often unable or unwilling to spend a lot of time on these programmes. Intervention meant to reduce fatigue should therefore be tailored to the survivors' needs, especially to the needs of young adult survivors of childhood cancer whose cancer treatment occurred far in the past. Studies of the exercise preferences of cancer survivors have shown that walking was their preferred daily physical activity and they preferred exercise at home.[16-18] With this in mind we designed an individualised exercise programme for enhancement of daily physical activity.

We hypothesized that severely fatigued childhood cancer survivors would be less likely to meet public health exercise guidelines (i.e. at least 150 minutes of moderate-to-vigorous exercise/wk) and that enhanced daily activity could realize an improvement in fatigue. Therefore the purpose of our study was to evaluate the effect of enhanced daily activity on fatigue in adult survivors of childhood cancer.

Study subjects

Adult survivors of childhood cancer were eligible when they were 18 years or older, 5 years or more post diagnosis, and participated in the long-term programme (LTFU) of the UMC Groningen, the Netherlands. They were sent information about the study by mail and invited to participate in this programme on cancer related fatigue. Exclusion criteria were: using a wheelchair, contraindications for exercise or severe cognitive impairment. To exclude potential seasonal influence on outcome of the CIS and to compare the CIS results of the survivors to those of healthy persons, 33 healthy age-matched controls (sibs and/or friends) were approached by the survivors and subsequently the investigators to complete the Checklist Individual Strength (CIS) to measure fatigue at the same time as survivors.

The study was approved by the UMCG review board. Written informed consent was obtained from all survivors and controls.

All survivors who were interested in the study were invited to fill in a Visual Analogue Scale for chronic fatigue (VAS fatigue) and a Stage of Change questionnaire. The VAS fatigue, which is a numerical measure ranging from 0-100 has been used to assess fatigue in cancer survivors. Survivors with a fatigue score of 70 or higher were classified as suffering from severe fatigue and showed a dramatic decrease in physical functioning.[19,20] Therefore, we used a score of 70 mm or more on the VAS as an inclusion criterion. The Stage of Change questionnaire was used to evaluate to what extent survivors met public health exercise guidelines (i.e. at least 150 minutes of moderate-to-vigorous exercise/wk). The SOC questionnaire is also helpful for the counsellor to adjust his approach.

Measuring instruments

Visual Analogue Scale for chronic fatigue (VAS fatigue)

A Visual Analogue Scale for fatigue (VAS fatigue) is designed to measure the characteristic fatigue, that is believed to range across a continuum of values and cannot easily be measured directly. Operationally, the VAS is a horizontal line, 100 mm in length, anchored by word descriptors at each end. In our study the descriptors ranged from 'not tired at all' to 'completely exhausted'. The patients were requested to mark on the line the point that they felt best represented their perception of their current state. The VAS fatigue score was then determined by measuring the distance in millimetres from the left-hand end of the line to the mark.

The Stage of Change questionnaire (SOC)

The SOC is based on the Stages of Change Model developed by Prochaska and DiClemente.[21] This model suggests that people adjust their behaviour in five stages. People in stages 1–3 are sedentary. Those in stages 2 and 3 are more likely to change their physical activity behaviour. People in stages 1 and 2 will benefit most from a daily activity stimulation programme.[22] Those in stages 4 and 5 do already meet public health physical activity guidelines and need different advice in how to enhance daily physical activity compared to those in stages 1,2 and 3.

All survivors who were interested in taking part in the study were asked to complete the Stage of Change questionnaire.

Checklist Individual Strength (CIS)

Fatigue was the primary outcome and it was measured with the CIS. The CIS is a validated 20-item questionnaire, that is designed to measure four aspects of fatigue that may have been experienced during the previous 2 weeks, i.e. severity of fatigue (8 items), concentration (5 items), motivation (4 items) and physical activity (3 items). Each item is scored on a 7-point Likert scale. The total score is the sum of the scores 1-7 on the 20 items (range 20-140). Norm scores are available for different patient groups and healthy people. Based on scores in healthy controls a score on the subscale 'fatigue severity' between 27 and 35 indicates an increased experience of fatigue. A score of 35 or higher indicates severe feelings of fatigue.[23 24]

Pedometer (Yamax digiwalker SW-200®)

As Tudor-Locke et al. have shown that a pedometer is helpful to provide feedback to those who use it, that it helps them to extend their daily activities and to set specific goals[25,26], we used a pedometer to measure the number of daily steps. The Yamax digiwalker SW-200®, has been shown to be one of the most reliable pedometers.[27,28] The instrument is worn on the belt or waistband and responds to vertical accelerations of the hip during walking. The non-ambulatory daily physical activities like swimming, cycling, weight lifting and so on are converted based on the intensity of this physical activity calculated in Metabolic Equivalents in minutes (METS min). For example: one minute cycling, swimming is about 150 steps.[29] The number of steps was registered in a step diary, either online or by posting their diaries, at start, in week 4 and week 10 (Figure 1).

Methods

The study design is summarised in Figure 1.

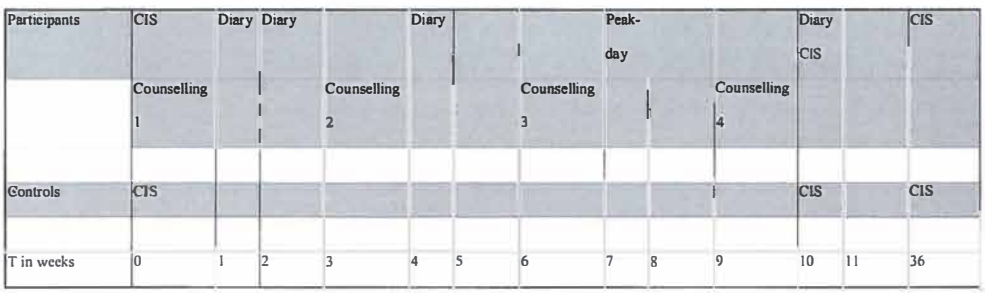
The counsellor (MB) encouraged participants to change their lifestyle and enhance daily physical activity such as walking, cycling, housekeeping and gardening. The pedometer was used as feedback instrument to give the survivors insight in their daily physical activity, to help them to extend their daily activities and to set new goals.

The counsellor was trained according to the COACH protocol (www.coachmethode.nl).

Table 1: Topics discussed by the counsellor at the start of the study

1.	How the pedometer works
2	How to record the daily steps and other daily physical activity on the specially developed website or in the diary
3	An information leaflet on how to increase daily physical activity and develop a physically active lifestyle
4	Participants were asked to use a pedometer for two weeks maintaining their normal daily physical activities as usual, and record their steps in a diary on the website or by posted diaries. Baseline step monitoring was used to assess baseline daily physical activity
5	Participants were asked to complete a CIS questionnaire and to find a relative or friend who would also be willing to complete this questionnaire at three different moments during the study
6	Participants were shown how to keep in contact with the counsellor by e-mail or telephone

Figure 1: Study design



CIS : Checklist Individual Strength

This method is based on the Motivational Interviewing Technique created by Miller and Rollnick and the goal-setting theory developed by Locke and Lathem, both considered to be effective instruments for behavioural modification.[30,31]

At the start of the programme survivors were visited at home by the counsellor, who explained the use of the pedometer and the step diaries (Table 1). They were asked to complete the CIS questionnaire and to invite a sibling or peer of the same age as a control person for the CIS questionnaire. The controls completed the CIS on the same time as the survivors but did not use the pedometer. The survivors wore a pedometer during two weeks at start to assess steps at baseline and in week 4 and 10 during the study (Figure 1). At the end of each day, participants had to record daily step counts and duration in minutes of other activities, in either an online step diary or a posted diary.

At three weeks, six weeks and nine weeks the counsellor phoned the survivors. The SOC results helped the counsellor to know in what stage the survivor is so his approach can be adjusted accordingly. Those in stages 2 and 3 are more likely to change their physical activity behaviour. Those in stages 4 and 5 do already meet public health physical activity

guidelines and need different advice in how to enhance daily physical activity compared to those in stages 1,2 and 3.

At three weeks the use of the pedometer and the diary were evaluated and the results of the baseline measurement was discussed. Survivors were asked by how many steps they thought they could improve. Together with the counsellor, a new goal was set for the next appointment. All participants received a written summary of the telephone conversation and were asked to wear the pedometer again in week 4, recording their steps in the diary. After six weeks the counsellor and the participant evaluated whether the goals set had been accomplished, and if not, the specific barriers were discussed. In some cases it was necessary to adjust the goal to a lower number of steps per day. Participants were asked to plan a 'peak day'. This was to be a day when circumstances were favourable (e.g. nice weather, shopping with a friend, etc.). On the peak day the survivor was supposed to take as many steps as possible. All survivors received a written summary of the telephone conversation and were asked to wear the pedometer on a peak day in week seven, recording the number of steps taken on this day in the step diary. After nine weeks the counsellor evaluated the 'peak day' and discussed with the survivors whether they thought it possible to adjust their goals to a higher number of steps per day. All participants received a written summary of the telephone conversation, and were asked to wear the pedometer in week ten, recording their steps in the step diary. Survivors and controls were asked to complete a CIS questionnaire at the end of the programme in week 10 and again in week 36 to assess if the assumed effect on fatigue would hold after termination of the counselling.

Statistics

A power analysis was calculated, with an alpha of 0.05 and a power of 0.80. Assuming a correlation of 0.70 between successive measures and a standard deviation of 20 meant that if 50 survivors and controls participated, a decrease of nine points on the CIS (between baseline and end) could be detected in the participant group compared with controls. We assumed that the CIS outcomes of the control group would not change. A general linear model for repeated measures (GLM) was used to compare the CIS results of survivors and controls over time (baseline, 10 weeks and 36 weeks). A 'repeated' contrast was used to investigate the significance of each measurement compared to the subsequent measurement. A general linear model for repeated measures was also used to study the change in daily physical activity (baseline, 3 weeks and 10 weeks) for the survivors. A linear regression analysis was used to analyse the relationship between the change in CIS score and the change in daily physical activity. A p-value less than 0.05 was considered significant. SPSS 15 was used to perform the analyses.

RESULTS

Four hundred and eighty six survivors were eligible and were sent a letter to inform them of the study; initially those who replied (453/486), were sent the VAS and the SOC questionnaire. The response rate was 56% (254/453). Sixty-seven survivors had a VAS score of ≥ 70mm, of these 67 qualifying survivors 21 refused participation for several reasons. Finally, 46 were enrolled in the study, but eight dropped out during the study. Descriptive characteristics of the survivors who entered the study at start are shown in Table 2. No statistically significant differences in age, cancer diagnosis and treatment between participants and non-participants were found. The median age at the study was 29 (range 18–61). Leukaemia was the most common diagnosis (46.8%).

Table 2: Characteristics of the participants

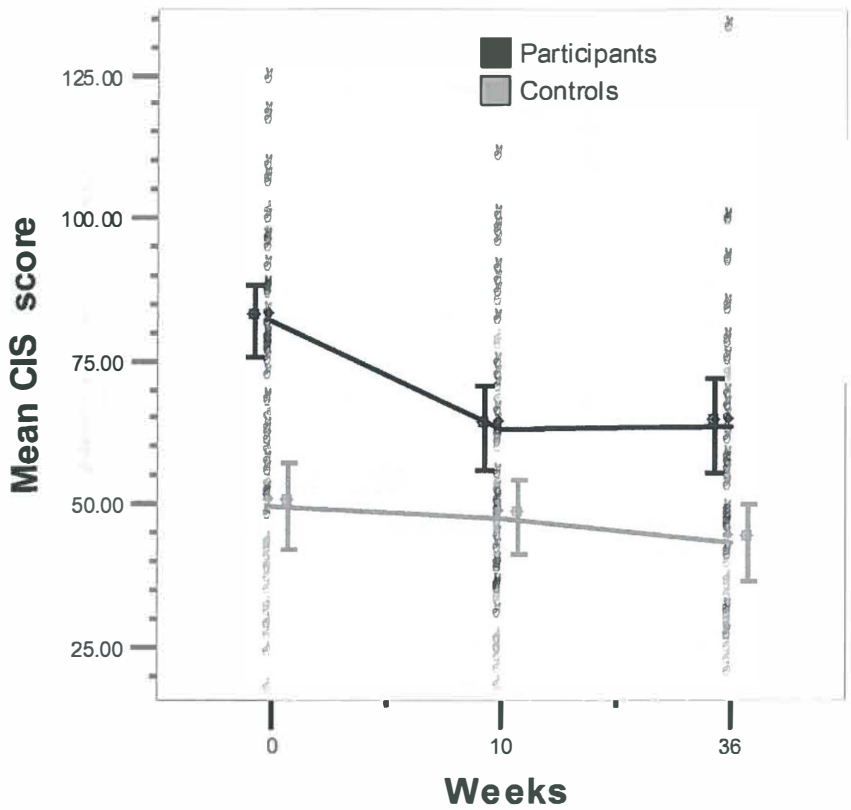
	Participants (n = 46)
Age (years)*	29.8 ± 8,6
Age at diagnosis (years)*	8.1 ± 6.7
Time since diagnosis*	21.8 ± 7.1
Male gender**	14 (30.4)
Diagnosis**	
Leukemia	22 (46.8)
Malignant lymphoma	6 (12.8)
Bone tumour	4 (8.5)
Soft tissue sarcoma	3 (6.4)
Wilms' tumour	1 (2.1)
Langerhans cell histiocytosis	2 (4.3)
CNS tumour	6 (12.8)
Other	3 (6.4)
Treatment**	
Chemotherapy only	22 (47.8)
Surgery only	2 (4.4)
Radiotherapy only	0 (0)
Chemo and radiotherapy	22 (47.8)
Cranial radiation	12 (26.1)

*Median ± SD
** Number (percentage)

The Stage of Change questionnaire (SOC)

Out of 453 survivors who were interested in the study 251 childhood cancer survivors returned the SOC, 140 (56%) survivors did not meet public health exercise guidelines (i.e. at least 150 minutes of moderate-to-vigorous exercise/wk)[32]. Out of the 46 participants, 36 (78%) did not meet public health exercise guidelines. The 46 participants were more likely (78%) to be in one of the three lower scales of the SOC questionnaire than the total group of survivors who completed this questionnaire (56%).

Figure 2 Changes in mean CIS scores during study period

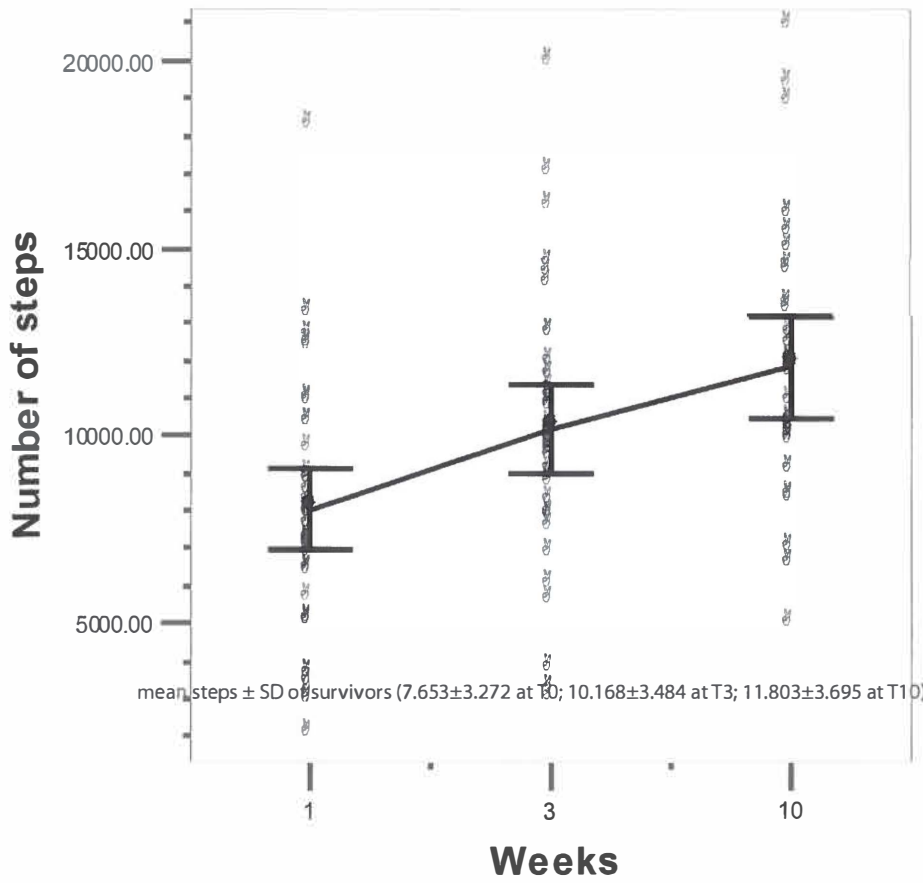


Participants (N=33)			
Mean (SD)	81.42 (±20.14)	62.62 (±20.86)	63.67 (±23.12)
Controls (N=28)			
Mean (SD)	47.39 (±19.06)	46.18 (±17.70)	42.57 (±17.40)

(CIS: Checklist Individual Strength)

(Lines connect means, error bars represent 95% CI)

Figure 3: Increase in number of steps during study period



(Lines connect means, error bars represent 95% CI, mean steps ± S D of survivors (7.653±3.272 at T0; 10.168±3.484 at T3; 11.803±3.695 at T10)

Fatigue

GLM analysis showed a significant interaction between time and group ($F = 7.5$, df 2.58, $p = 0.001$). The mean scores on the CIS in the survivors were 81.42 ± 20.14 at T0 and 62.62 ± 20.86 at T10, which was a significant improvement ($F = 19.7$, df 1.59, $p < 0.0005$). At T36, the mean CIS score was 63.67 ± 23.12, which was a significant improvement compared to the mean CIS at the start ($F = 17.8$, df 1.59, $p < 0.0005$). Controls had a mean score of 47.39 ± 19.06 at T0, of 46.18 ± 17.70 at T10 and of 42.57 ± 17.40 at T36.

This was significantly different ($F = 29.7$, df 1.59, $p < 0.0005$) from the mean CIS scores at T0, T10 and T36 of the survivors. There was no statistically significant difference in the mean CIS scores of the controls during the study period (Figure 2).

Daily physical activity (steps per day)

GLM analysis showed a significant increase in daily physical activity (steps per day) during the first ten weeks ($F = 16.7$, df 2.30, $p < 0.0005$). At T0 the mean number of daily steps

in the participant group was 7.653 ± 3.272. After the first telephone session (T3) with the exercise counsellor there was an increase in the number of steps per day to 10.168 ± 3.483, which is an increase of 33%. At T10, after the third telephone session, when participants were asked to adjust their goals, the number of daily steps increased to 11.803 ± 3.695. This increase is statistically significant compared to the number of steps at T0 ($F = 32.0$, df 1.31, $p < 0.0005$) and T3 ($F = 10.4$, df 1.31, $p = 0.003$). From the start until the end of the intervention (ten weeks) there was an increase in daily steps of 54% (Figure 3). Although the number of daily steps increased during the study period there was a low correlation of 0.12 between the increase in daily steps (T10 minus T0) and the decrease in fatigue (T10 minus T0).

DISCUSSION

In this study the effect of a home-based daily physical activity counselling programme – with feedback from a pedometer – on fatigue in adult survivors of childhood cancer was evaluated. It was shown that such a programme was effective in decreasing fatigue in adult survivors of childhood cancer during at least a 36 weeks period. We found not only a statistically significant improvement in fatigue but also a statistically significant increase in daily physical activity, measured in steps per day by a pedometer. These results are in accordance with those of Blok et al [33] who showed that the use of a pedometer in combination with exercise counselling is effective in increasing daily physical activity levels in COPD patients and of Tudor-Locke et al [34] in patients with type-2 diabetes. Other studies conclude that a physical activity programme which adjusts lifestyle is as effective as a structured exercise programme in improving the daily physical activity of adults.[35,36] However most studies have been done in breast cancer survivors[37-39] and in patients who have received stem cell transplants[40,41], whereas studies in childhood cancer survivors are limited.[42] We are not aware of other studies on the effectiveness of a physical activity counselling programme on fatigue in childhood cancer survivors.

Vallance et al. 2005[43] reported that Non-Hodgkin Lymphoma (NHL) survivors who met public health exercise guidelines had clinically and significantly higher QoL scores than survivors who did not meet these guidelines. In our study, 36 out of 46 participants (78%) did not meet public health exercise guidelines (i.e. at least 150 minutes of moderate physical activity per week).

Fatigued survivors represent a high-risk group as they report more depression and poorer Quality of Life (QoL) than non-fatigued survivors and their peers.[44] The aetiology of fatigue in (childhood) cancer survivors is still largely unknown. There is a relationship between depressive symptoms and fatigue.[44,45] The relationship is complex, as fatigue may be the result of a depressed mood, while at the same time a severely fatigued person may also

become depressed. Servaes and Van derWerf et al.[46] showed that in a group of severely fatigued cancer survivors, only 19% could be considered to be clinically depressed and 14% were clinically anxious. Regular exercise, even a moderate walking exercise programme has been shown to decrease anxiety and depression levels.[47] Whether the cause of fatigue in cancer survivors is related to depression or due to lack of physical activity, cancer survivors might benefit from regular exercise. For many years, physicians have recommended cancer patients that they should rest and avoid physical effort because exercise could generate symptoms such as fatigue.[48] However physical inactivity induces further muscular wasting and loss of cardio-respiratory fitness. This could explain the persistence of fatigue in some patients even years after the end of treatment.

When designing exercise programmes, it is useful that the preferences of individual survivors be taken into account; these preferences might change according to which stage of life they find themselves.[16,17]

Our study has several limitations. The sample size was small and the response rate of 56% was moderate. This may have led to a biased selection of participants. The value of a pedometer as an instrument to assess exercise might be questioned, as it is not sensitive to non-ambulatory physical activities such as cycling, swimming and fitness training (weight lifting). However a pedometer is cheap and easy to use, and therefore highly suitable for daily use. Because eight persons dropped out during the study, we did not include the 50 survivors as we intended at start but because the improvement in CIS scores was higher than expected the study had still enough power. The study was not randomised and controls did not use the pedometer.

CONCLUSION

The stimulation of physical activity using exercise counselling with feedback from a pedometer over ten weeks leads to a statistically significant improvement in fatigue in adult survivors of childhood cancer, and this improvement lasts for at least 36 weeks. A home-based daily physical activity programme, compared to the existing structured exercise programmes in rehabilitation centres, is cheap, less time-consuming and requires no special facilities. Therefore this programme might be more suitable for young adults who are busy starting careers and planning to have a family. Randomised controlled studies with larger numbers of participants are needed to confirm our preliminary results. A longitudinal study is needed to examine long-term effects in terms of a decrease in fatigue.

Acknowledgements

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CHAPTER 6

The willingness of general practitioners to be involved in the follow-up of adult survivors of childhood cancer

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ABSTRACT

Background: Long-term follow-up of childhood cancer survivors is mainly organised by paediatric oncologists and until now general practitioners (GPs) are rarely involved. To ensure appropriate follow-up for all survivors into adulthood, a combined effort of paediatric oncologists and general practitioners might be the solution. We investigated the willingness of GPs, who had followed a postgraduate course on late effects of cancer treatment, to participate in a shared care model for follow-up of adult childhood cancer survivors as well as what their requirements would be in case of participation.

Methods: From the Northern Netherlands, 358 GPs participated in a postgraduate course on late effects in paediatric cancer survivors. After the course, they were asked to complete a 10-item questionnaire on motivation to participate in the regular follow-up of adult childhood cancer survivors as well as their conditions to participate.

Results: The response rate was 65%. Of the responders, 97% were willing to participate in a shared care model for follow-up and 64% felt that it was their responsibility to be in charge of childhood cancer survivors. The main requirements for participation were the availability of guidelines (64%), sufficient information about the patient's medical history (37%), and short communication lines (45%). The main barriers to participate were workload (16%), lack of knowledge (15%), and lack of communication (13%).

Conclusion: A significant number of GPs are ready to participate in the long-term follow-up of adult childhood cancer survivors if adequate guidelines and medical information is provided and communication lines are clear.

INTRODUCTION

One of the growing challenges in medicine is providing appropriate health care for survivors of childhood and adolescent cancer. Childhood cancer is rare but major advances in paediatric cancer therapy have led to long-term survival of approximately 75% of children treated .[1] This success story has been tempered by the knowledge that cure has often come at a price, which may not be manifest until many years after therapy. Late or long-term effects are defined as persistent and adverse changes due to the disease and/or its treatment. Because childhood is a time of rapid physical growth and emotional development, the consequences of therapy can be far different from the results of similarly treated adults. It is estimated that physical and/or psychosocial complications may develop in as many as two-thirds of these young adults.[2]

Late effects vary in severity dependent on the specific type of cancer, treatment received, and the age of the child during therapy.

Because the population of adult survivors of childhood cancer is still relatively young, with only a small portion over the age of 40, there are only few data yet to answer the question if survivors of childhood cancer are at risk for prevalent diseases of middle to later life. In an earlier study we showed that the prevalence and the severity of late effects increased with time since diagnosis.[3] As time since diagnosis extends, medical problems associated with aging may exhibit an earlier onset or a more accelerated course following certain cancer therapies. Oeffinger et al.[4] described that cancer survivors, diagnosed with cancer between 1970 and 1986, were more vulnerable to diseases that are associated with aging, like second cancers, heart conditions, kidney disease, musculoskeletal problems, osteoporosis, and sterility compared with their siblings.

Only through long-term follow-up of adult survivors the impact of these types of iatrogenic late effects on the aging process will become evident, and thus we will be able to rationally determine long-term risk–benefit ratios. A systematic plan for lifelong screening, surveillance, and prevention that incorporates risks based on the previous cancer, cancer therapy, genetic predispositions, lifestyle behaviours, and co-morbid health conditions should be developed for all survivors.

The improvements in outcome have not been accompanied by equal progress in the manner in which care is provided to (young) adults with these conditions. It has been reported that less than 20% of adult survivors of childhood cancer are followed at a cancer centre or by an oncologist. As the number of survivors of childhood cancer is expected to increase further, there is some urgency in determining where long-term follow-up should take place.

It will be difficult for the usual paediatric oncology clinical services to accommodate the demands of the ever-enlarging population of survivors. Moreover, adult survivors do

not fit in paediatric clinics, thus transition of care from the paediatric to the adult health care setting is necessary for most childhood cancer survivors. By integrating general practitioners in the paediatric programs, a seamless transition from a predominantly paediatric-to a predominantly adult-oriented follow-up can be guaranteed.

Currently a typical general practitioner's practice will include about two to three adult survivors, but as the number of childhood cancer survivors increases, general practitioners will encounter childhood cancer survivors in their practices more often, up to eight to nine in 2010.[5] These survivors are a heterogeneous population with a variety of different cancers diagnosed at different age periods or different treatment protocols and recommendations for screening are continuously evolving. Thus it is understandable that general practitioners are not particularly aware of the risks of this population. Although there is considerable information available about long-term effects, most has been published in the paediatric or oncology literature. It is important to establish systems by which general practitioners become knowledgeable about the late sequels of cancer treatment and its consequences on adult health. Information materials need to reach primary care providers before their first interaction with a patient who is a childhood cancer survivor. The aim of this study was to investigate the views and needs of general practitioners on participating in a shared care program for the follow-up of adult survivors of childhood cancer.

METHODS

Bi-annual refresher courses have been organised for GPs in the Northern provinces of The Netherlands for more than 30 years. These 5 days courses are repeated for 3 or 4 weeks in succession; each course is attended by about 50 GPs. The program for these courses is defined by a committee of GPs. The courses invite lecturers who are experts in the selected subjects. These courses have established a good reputation and are attended by about two-third of all GPs in these provinces. One week prior to the onset of the course the attending GPs receive a syllabus on the specific topics. In 2005 and in 2006 a paediatric oncologist and a GP working at the Long-term Follow-up clinic (LTFU) of the UMC Groningen were invited to lecture on adverse late effects in childhood cancer survivors.

Late effects of treatment after childhood cancer were explained using case histories of childhood cancer survivors (Table 1). Shared care of paediatric oncologists and patient's own GPs was discussed as a possible model for the long-term follow-up of childhood cancer survivors. Low frequent visits to the LTFU clinic are combined with regular follow-up in the GP's practice. The screening in the GP's practice will take place after the GP had been extensively informed about the previous history and health risks by the LTFU clinic. GPs were requested to evaluate the lecture using a 1–5 scale [(bad)–(excellent)]. At the end of the course all 358 GPs received an envelop containing a 10-item questionnaire

Table 1. Content of lecture on late effects in childhood cancer survivors

	Content
Introduction	Most common adverse late effects after chemotherapy treatment in childhood cancer survivors
	Most common adverse late effects after radiation therapy in childhood cancer survivors
Case A: A 31-year-old man treated for Hodgkin Disease at age 12 with chest pain	Coronary artery disease after mediastinal radiation
Case B: A pregnant woman treated for Ewing Sarcoma at age 2 with i.a. anthracyclines, who desires to deliver at home	Cardiotoxicity after treatment with anthracyclines
Case C: A 35-year-old woman treated for childhood cancer with irregular menstrual cycle	Immature ovarian failure and premature menopause
Case D: A 27-year-old man treated for ALL at age 7 with cranial radiation and now having epileptic insults	Risk of second malignancies
Case D: Same case as above 2 years later presenting with fatigue and metabolic syndrome	Growth hormone deficiency and risk for metabolic syndrome
The need for long-term follow-up and the role of the GP	Low frequent controls in the LTFU clinic, combined with regular follow-up in the GPs practice as a new model for long-term follow-up

(Table 2) and were asked to return it by mail within 2 weeks to assess their opinion about shared care as a future plan for the follow-up of adult childhood cancer survivors. They were asked what their main requirements and barriers were. Also questions were asked about compensation, electronical forms and the role of a practice assistant in the screening process. These answers were plotted on a seven-point scale (most important–not important at all). The answers on the open questions 'If you were asked to participate in a shared-care program for the follow-up of adult childhood cancer survivors what would your requirements be?' and 'If you were asked to participate in a shared-care program for the follow-up of adult childhood cancer survivors what would your reservations be?' were categorized in seven respectively six different categories (Figs. 1 and 2).
Data were analyzed using SPSS 14 which generated descriptive statistics.

RESULTS

In 2005 and 2006, 358 GPs out of a total of 507 (71%) from two northern provinces in the Netherlands attended the refresher course. The response rate was 65% (233 out of 358 questionnaires; Table 2). The overall lecture was evaluated as a mean 4.51 (SD 0.54) for the content and an mean 4.23 (SD 0.56) out of 5 for the presentation. On the question 'if you were asked to participate in a shared care program with the department of paediatric oncology

Table 2 Content of questionnaire

Questionnaire	Response rate 65%
Willing to participate in a shared care program with the department of paediatric oncology for the follow-up of adult survivors of childhood cancer	Yes No
Willing to participate in a shared care model for follow-up	
Yes, because:	Responsibility to be in charge for childhood cancer survivors
	Few patients, less time consuming
	Consider these patients as special
	Gain more knowledge
No, because (not specified)	
Compensation for GPs should depend on returning the records to improve the motivation of GPs to return records	7-point scale of importance
Keep records used for screening simple	7-point scale of importance
Possibility of returning the forms electronically	7-point scale of importance
The practice assistant should be involved in the follow-up care	7-point scale of importance
If you were asked to participate in a shared-care program for the follow-up of adult childhood cancer survivors what would your requirements be?	Open-ended question
If you were asked to participate in a shared-care program for the follow-up of adult childhood cancer survivors what would your reservations be?	Open-ended question

for the follow-up of adult survivors of childhood cancer 97% (225/ 233) answered positive. About 64% (150/233) of the GPs thought that participating would be a normal part of the care that GPs ought to provide. About 66% (154/233) of the GPs thought participating would not be very time consuming because they have only few adult paediatric cancer survivors in their practice. Seeing these patients as special (161/233) and to gain more knowledge were given as a reason to participate in approximately 70% (164/233) of the GPs. Only seven GPs (3%) refused.

Reasons for not wanting to participate were: lack of time (n=4), negative experience with collaboration with specialists in the past (n=1), considering it a task for the specialist (n=1), and one GP did not give a reason for refusing to participate. Approximately 37% (85/233) of the GPs thought that rewarding the GPs before they had returned the results of the screening to the department of oncology to improve the return rate was important, 40%

Figure 1 If you participated in follow-up what would be your requirements (%)?

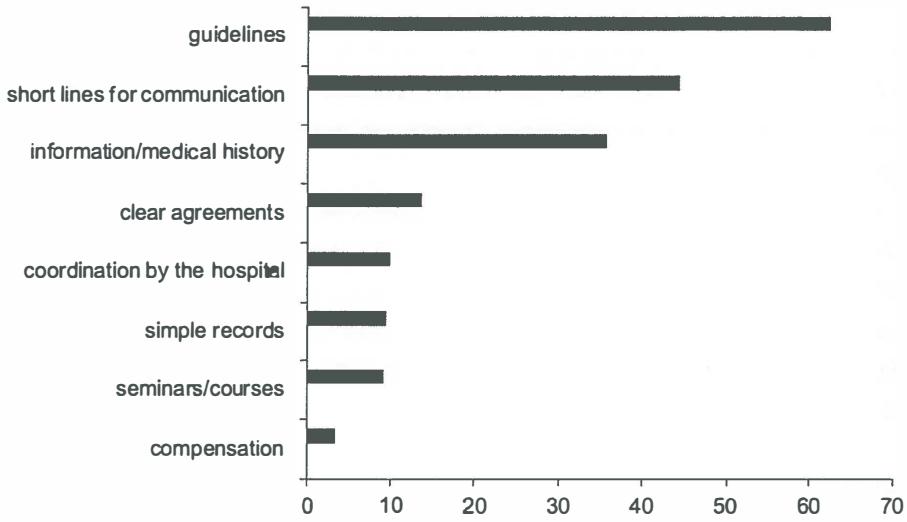
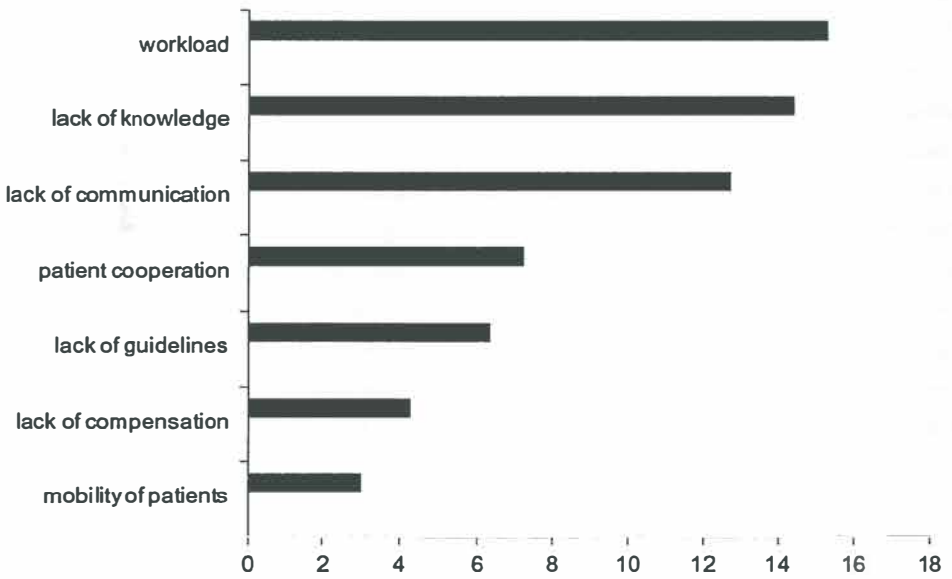


Figure 2 If you were asked to participate in follow-up what would be your reservations (%)?



(93/233) thought this was not important, and 23% (55/233) had no opinion. To keep the records simple was important for 96% (223/233) of the GPs. Almost half (110/233, 47%) of the GPs found it important that the forms could be returned electronically. Of the 206 GPs who had a practice assistant only 16% (33/206) thought it was important that the practice assistant should be involved in the follow-up care and only 13% (27/206) thought it was important that the practice assistant should be responsible for returning

the records of the screening to the LTFU clinic. The two open questions were 'If you were asked to participate in a shared-care program for the follow-up of adult childhood cancer survivors what would your requirements be?' and 'If you were asked to participate in a shared-care program for the follow-up of adult childhood cancer survivors what would your reservations be?' The answers were categorized in seven respectively six different categories (Figs. 1 and 2).

Clear guidelines (148/233, 64%), short lines for communication (106/233, 45%), and clear information about patient's medical history (86/233, 37%) are the main requirements for participation. The main barriers to participate were: workload (36/233, 16%), lack of knowledge (34/233, 15%) and lack of communication (30/233, 13%) between GPs and paediatric oncologists. Lack of compensation was only a barrier to participate for 4% (10/233).

DISCUSSION

There is consensus that the primary treatment of childhood cancer requires specialized care, and a plan for follow-up should be available for all survivors of childhood cancer. However, it is unclear whether oncology-based follow-up care is the appropriate model of care to meet long-term needs of survivors of childhood cancer. This study shows that adequate guidelines and medical information, as well as clear communication lines are important for GPs to participate in the long-term follow-up of adult childhood cancer survivors. These findings are confirmed in other studies.[6,7]

The combined efforts of paediatric oncologists and general practitioners will be important during the next decades to observe and report the life-long effects of treatment and lifestyle on survivors.[8] Models of shared care have been developed for chronic diseases such as diabetes, hypertension and asthma, and there are some examples of shared oncological care.[9-11] Some studies suggest that GPs are willing to become engaged in the follow-up care of cancer patients and that hospital follow-up provides no advantages compared to follow-up in primary settings .[12,13]

Because of the relative rarity of childhood cancer GPs lack knowledge of cancer related health risks.[14] This evaluation indicated that GPs appreciate postgraduate courses about adverse late effects, even though childhood cancer survivors represent a very small portion of individual GP practice. Whether actual practice behaviour changes will follow such a course should be studied in the future. Involving GPs in a shared-care model for the follow-up of adult childhood cancer survivors will increase the GP's knowledge for sequelae of cancer treatment in general and this could potentially benefit many types of cancer survivors. Shared care in oncology remains controversial. It is often promoted as offering patients care closer to home while, at the same time, reducing the burden on

specialist services. GPs are divided on the issue, some viewing shared care as improving job satisfaction and others as another example of hospitals offloading work onto an already overloaded primary care sector. For the success of a shared care program it is important that GPs see the program as a step up from 'usual' care in general practice rather than a step down from hospital practice.[15]

Summary of main findings

This study showed that the great majority of the attending GPs (97%) are ready to participate in a shared care model for the long-term follow-up of adult paediatric cancer survivors and 64% of them state that participating would be a natural part of the care they provide.

It is interesting that when they were asked about their requirements in order to participate compensation was only important for 4% of the GPs. To make sure that GPs return the records of the screening to the LTFU clinic it is important to keep the records as simple as possible and it is worthwhile to consider if electronic exchange of information is possible as 47% of the GPs said that this way of exchange has their preference.

There seems not to be an important role for the practice assistant in the follow-up of adult survivors of paediatric cancer according to the views of GPs. Comments made about the role of the practice assistant were that they have a role in routine care for larger patient groups like diabetes but not for the special care these cancer survivors need.

Limitations

Because of the fact that most GPs are not acquainted with the issue of late effects in childhood cancer survivors, we decided to send the questionnaire to GPs who had been informed about this issue and about the shared care model as a possible model for the follow-up of adult childhood cancer survivors and not to representative groups from the entire country. The 1-week refresher course for GPs contains several health subjects and prior to registration attending GPs are not aware of the topics so they had no prior idea that adverse late effects in childhood cancer survivors would be one of the topics covered. From the two provinces where the study was conducted, 29% of GPs did not attend the course and therefore did not have the opportunity to participate. Furthermore 35% of those who attended the course did not complete the questionnaire and this might have led to a selection bias. Giving a course about late effects to the GPs prior to the completion of the questionnaire might have influenced the outcome positively. This could explain that the number of GPs willing to participate in the long-term follow-up of childhood cancer survivors (97%) is much higher than the number of GPs willing to participate in the follow-up of patients with colorectal cancer (50%) .[6]

Although we cannot be sure whether our findings can be generalized for the entire

Netherlands, there is no reason to believe that there will be significant differences in the attitudes of GPs in the North from those in the rest of the country. We also think that our findings go for countries where the health care system shows great resemblance to the Netherlands such as England, Flanders and the Scandinavian countries. We recognize the relative weakness of lack of validation of our questionnaire. By using open ended questions for the requirements and objections of participating we left the possibility for participants to individualize their own comments. We therefore believe that our questionnaire is reliable enough to represent the views of the GPs. Berendsen et al.[7] showed that 'developing personal relationships', 'gaining mutual respect' and 'increasing medical knowledge to the benefit of their patients' are the most important motivational factors for GPs for new collaboration models with medical specialists.

Implications for future research or clinical practice

We believe that follow-up care as a coordinated effort of the paediatric oncologist and the general practitioner could be used for the follow-up of adult childhood cancer survivors and should be further studied. Such a shared-care model could facilitate the necessary transition from paediatric-based care to adult care as childhood cancer survivors mature into adulthood. An example would be regular visits to the long-term follow-up clinic (LTFU) till the age of 18–21 years with transfer to a shared-care follow-up program in which the patients GPs are involved. The LTFU clinic has to support the GP continuously with specific guidelines and management of late effects and will see the patients on a low frequency base according to their individual risk profile. The corner stone of shared care is personal communication and provision of adequate guidelines.

We conclude that a significant number of GPs are ready to participate in the long-term follow-up of adult survivors of childhood cancer if guidelines and medical information provided and communication lines are clear; whether they perform adequately needs further study.

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CHAPTER 7

Shared care by paediatric oncologists and family doctors for long-term follow-up of adult childhood cancer survivors: a pilot study

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ABSTRACT

Background Since 75% of children with cancer will become long-term survivors, late effects of treatment are an ever increasing issue for patients. Paediatric oncologists generally agree that cancer survivors should be followed up for the remainder of their lives, but they might not be the most suitable health-care providers to follow up survivors into late adulthood. We designed a 3-year study to assess whether shared-care by paediatric oncologists and family doctors in the long-term follow-up of survivors of childhood cancers is feasible, whether a shared-care model is compatible with collection of data needed for registration of late effects, and how a shared-care model is assessed by survivors and family doctors.

Methods In 2004 and 2005, adult survivors of childhood cancers were randomly chosen from eligible patients diagnosed with childhood cancer (excluding CNS tumours) or Langerhans-cell histiocytosis between January, 1968, and December, 1997, and recalled to the long-term follow-up (LTFU) clinic at the University Medical Centre Groningen, Groningen, Netherlands, where they underwent physical and clinical assessments by an on-site family doctor (visit 1). At this visit, assessments were done according to guidelines of the UK Children's Cancer Study Group Late Effects Group, and late effects were graded by use of Common Terminology Criteria for Adverse Events (version 3). Follow-up assessments were done 1 year later in 2005 and 2006 by local family doctors (visit 2), who were asked to return data to the LTFU clinic. At this visit, the local family doctors were asked to complete a three-item questionnaire and patients were asked to complete a seven-item questionnaire about their satisfaction with the shared-care model. At the next consultation, which was planned for the end of the study (visit 3), the on-site family doctor advised patients about future follow-up on the basis of their individual risk of late effects. Main endpoints were numbers of participants, satisfaction ratings, and proportions of local family doctors who returned data that they obtained at visit 2 to the LTFU clinic.

Findings 133 individuals were chosen at random from 210 enrolled adult survivors. 123 of 133 (92%) randomly selected survivors and 115 of 117 (98%) of their family doctors agreed to participate in the shared-care programme. 103 of 115 (90%) family doctors returned data to the LTFU clinic at visit 2.

89 of 101 (88%) of survivors were satisfied with this shared-care model, as were 94 of 115 (82%) family doctors; 18 of 115 (16%) family doctors had no views either way; and three of 115 (3%) family doctors were dissatisfied.

Interpretation Shared-care by paediatric oncologists and family doctors is feasible for long-term follow-up of adult survivors of childhood cancers.

INTRODUCTION

Most children with cancer will become long-term survivors and many of them will be at risk of treatment-related adverse health outcomes. Estimations suggest that physical or psychosocial complications will develop in as many as two-thirds of these survivors. The severity of these complications vary from mild to severe, and might even be life-threatening.[1,2] 10% of survivors will die within 20 years of the end of treatment, some because of recurrence of primary disease, and others because of complications of previous treatment.[3] To enable survivors to enjoy the best quantity and quality of life, identification and treatment of late effects as early as possible is important.[4]

For a long time, the discharging of paediatric patients with cancer after a disease-free interval of around 10 years was common practice. Nowadays, paediatric oncologists world-wide believe that a systematic plan for life-long screening and surveillance should be offered to all survivors.[5,6] Much effort is being invested in the development of guidelines for assessment of late effects of cancer treatment, such as the guidelines of the US Children's Oncology Group, the UK Children's Cancer and Leukaemia Group (CCLG), and the Scottish Intercollegiate Guidelines Network (SIGN). Up to now, many adult survivors are not being followed up on a regular basis.[7] Of those who participate in follow-up programmes of childhood cancer, more than 90% are followed up by a paediatric oncologist in a paediatric institution.[8] However, paediatric oncologists are not the most appropriate health-care workers to care for survivors into late adulthood. Patients who have been treated for cancer might have ongoing complex health needs and many comorbidities that need a range of approaches provided through general practice. In the Netherlands, survivors usually have family doctors, most of whom are willing to participate in a shared-care programme.[9] In a shared-care programme, family doctors participate in the screening of late effects in adult survivors of childhood cancers in consultation with paediatric oncologists of the LTFU clinic.

Since the number of survivors of childhood cancers is expected to increase, identifying who should undertake long-term follow-up of such patients after achieving adulthood is important. Hospital-based life-long follow-up for all adult survivors will not only be very expensive, but also difficult to organise because of the ever-increasing population. From an economic point of view, we have to look for alternative follow-up programmes with the lowest burden, not only for survivors, but also for the expanding health-care budgets in many western countries. Family doctors will treat increasingly more of these patients, with a mean of eight or nine patients who survived childhood cancers registered with every family doctor predicted by 2010 (on the basis of a mean of 2350 patients registered for every family doctor).[10] If guidelines and ongoing supervision were made available from clinics such as the long-term follow-up (LTFU) at the University Medical Centre Groningen

(Groningen, Netherlands), the assessment of late effects could be undertaken by family doctors. If serious late effects, such as cardiac or endocrine complications were detected, survivors could be referred to an appropriate consultant. Involvement of family doctors in shared-care programmes for long-term follow-up would increase their knowledge about the unique needs of survivors of childhood cancers.

To assess shared-care by family doctors and paediatric oncologists in long-term follow-up of survivors of childhood cancers, we designed a 3-year study to assess whether such a model is feasible, whether shared-care is compatible with collection of data needed for registration of late effects, and how a shared-care model can be assessed by survivors and family doctors.

METHODS

Patients

210 adult (ie, aged 18 years or over) survivors were enrolled into the study. Patients were randomly chosen by use of a computer program and recalled to the LTFU clinic in the first year of the study and were eligible if they had been treated at the paediatric oncology department of the University Medical Centre Groningen (Groningen, Netherlands) at least 5 years previously and were not involved in any childhood cancer follow-up programme. Patients who were diagnosed with childhood cancer or systemic multifocal Langerhans-cell histiocytosis (LCH) between January, 1968, and December, 1997, were included. Patients with tumours of the central nervous system were excluded because most of them were being followed up by a multidisciplinary neuro-oncology team.

Procedures

In 2004 and 2005, survivors were recalled to the LTFU clinic at the University Medical Centre Groningen (Groningen, Netherlands; visit 1). An on-site family doctor with a special interest in late effects and who was employed by the LTFU clinic assessed the patients. Since Dutch guidelines were still under development at the time, the on-site family doctor used guidelines of the UK Children's Cancer Study Group (UKCCSG) Late Effects Group[11] to assess the survivors. Previous diagnosis and treatment established patients' risk-based assessments—eg, hormonal assessments, echocardiography, bone-mineral-density tests, or pulmonary-function tests. Late effects were graded by use of Common Terminology Criteria for Adverse Events (CTCAE; version 3).[12] CTCAE grades adverse effects from 0 to 4. Grade 1 effects are small and usually asymptomatic. Grade 2 effects are moderate, usually symptomatic, but do not impair daily activities. Grade 3 effects are severe and need more serious interventions. Grade 4 effects are potentially life-threatening. Health-related quality of life (HRQoL) at visit 1 (and also later at visit 3) was assessed by the RAND

36-item health survey (RAND-36). RAND-36 is an internationally used validated, reliable, generic self-report questionnaire that has been translated into Dutch[13] and validated for the Dutch population.[14] RAND-36 contains eight subscales: physical functioning, social functioning, role limitations due to physical difficulties, role limitations due to emotional difficulties, mental health, vitality, bodily pain, and general-health perceptions. For each subscale, scores were coded, summed, and transformed to a scale from 0 (worst health) to 100 (best health). The control group for the HRQoL analyses consisted of 1036 people aged 18 years and over who took part in a previous health screening of the population of Emmen in The Netherlands.[15] From the control group, mean scores of the subgroup aged 25–44 years (n=416) were used as reference values in our study. RAND-36 has been used in other studies to assess HRQoL in survivors of childhood cancers.[16,17] Follow-up of the assessed survivors was 1 year after their first visit, in 2005 or 2006 (visit 2), and was undertaken by local family doctors who had been sent information (from the on-site coordinating family doctor at the LTFU clinic) about patients' histories, health risks, and necessary tests. Survivors were sent letters asking them to make appointments of at least half an hour with their family doctors. The letters were accompanied by forms that were to be completed by the family doctors during the physical assessments at visit 2 (there were two forms: one for medical history and one for physical assessment). To maintain a complete survivor database in our hospital, family doctors were asked to return these forms and the results of their tests. We assessed this shared-care model with a three-item questionnaire for family doctors that asked whether the information they had received from the LTFU clinic was sufficient to do the screening, whether they were satisfied with the collaboration, and whether they had any suggestions to improve the collaboration; survivors were also asked to complete a seven-item questionnaire about their views on their follow-up by use of a five-point Likert scale for their answers, ranging from very satisfied to very dissatisfied.

At the next consultation, which was planned 1 year after visit 2, in 2006 or 2007 (visit 3) and was done by the onsite family doctor at the LTFU clinic, survivors were advised about future follow-up on the basis of their individual risk of late effects. Survivors were divided into three groups as described by Wallace and colleagues.[18] First, those with very low risk of future effects were to be followed up by a yearly health questionnaire by post that would be assessed by staff at the LTFU clinic. Second, survivors with moderate risk of late effects (ie, those who received chemotherapy or low-dose radiation) were to be assessed yearly by local family doctors, and fast and direct methods of communication (ie, email or telephone) to one member of staff at the LTFU clinic were suggested. Third, survivors with high risk of severe late effects— including those who had received moderate-to-high doses of radiotherapy, underwent bone-marrow transplantation, or received mega therapy (ie, intensive high-dose treatment)—were to be followed up in a shared-care

model as described earlier in this report. Many of these high-risk survivors would also need care by specialists, such as endocrinologists, cardiologists, and orthopaedic surgeons.
To justify the conclusion that this model is feasible for the long-term follow-up of adult survivors of childhood cancers, proportions of participants (ie, survivors and family doctors), satisfaction, and numbers of those who returned data should be high—as close to 100% as possible. The study did not need ethics or approval from an institutional review board or patients' written consent.

Statistical analyses

Data were analysed by descriptive techniques that used frequencies, percentages, means, and medians as appropriate. One-sample t test was used to compare the mean RAND-36 scores of the study group with the mean scores of the Dutch norm (reference) group. Paired-sample test was used to compare the mean RAND-36 scores at the start (visit 1) and at the end (visit 3) of the study. Since the total study sample was small, differences between cancer types were not analysed. A significance level of α=0·05 was applied in all analyses. Analyses were done with SPSS for Windows (version 14.0).

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, interpretation, or writing of the report. WT had access to the raw data. RB had full access to all the data and had final responsibility for the decision to submit for publication.

RESULTS

Of 210 enrolled adult survivors, 133 individuals were chosen at random and recalled by letter to the LTFU clinic in the first year of the study (visit 1; figure). The participants included eight bone-tumour survivors (osteosarcoma or Ewing sarcoma) who were older than 18 years at diagnosis and who had been treated when chemotherapy for osteogenic sarcoma was given by paediatric oncologists. Ten out of the 133 (8%) invited survivors refused for the following reasons: one patient was severely mentally retarded; two patients had an anxiety disorder and were afraid to return to the hospital; and the other seven patients felt well but did not wish to look back at their cancer experience. Therefore, 123 (92%) survivors agreed to take part in this study. Six of these survivors agreed to participate in follow-up, but were not prepared to attend the clinic visits and requested that all assessments were done by local family doctors. Although these six individuals had all three visits at their local practice, they were included in this study. 115 of 117 (98%) of the approached local family doctors (some had more than one patient) were willing to collaborate in the shared-care model, and two (2%) doctors refused (the two patients

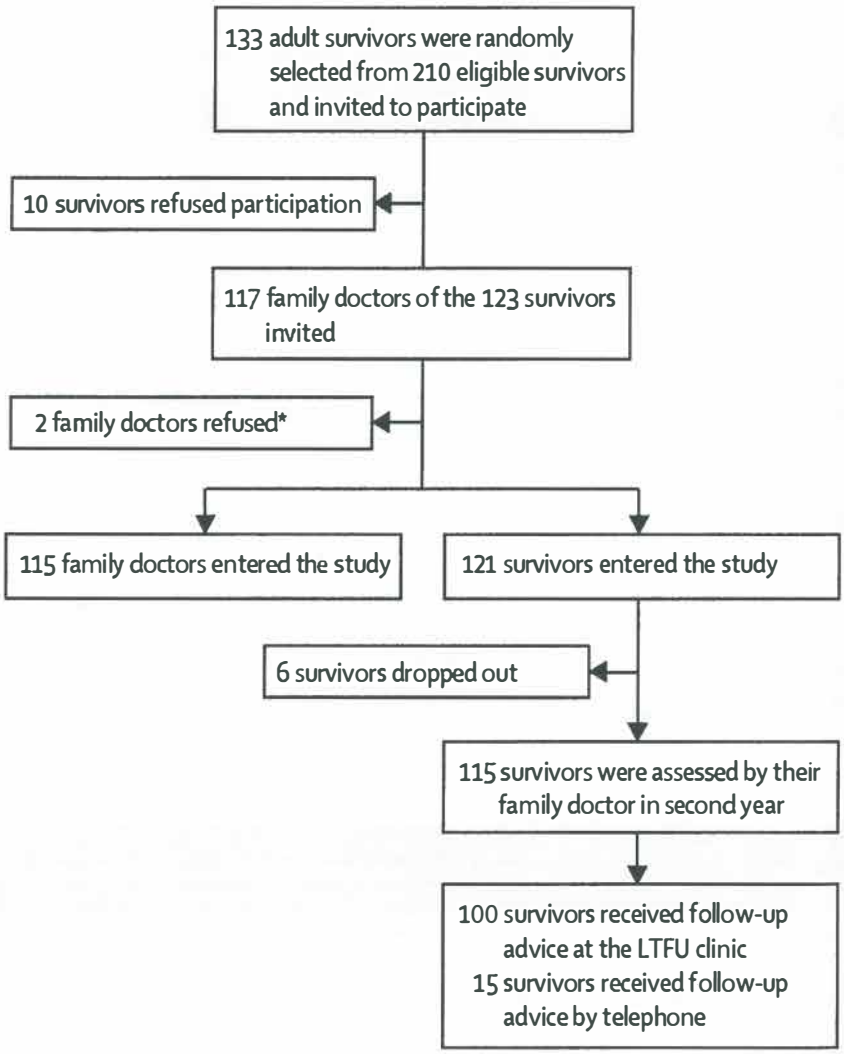
133 adult survivors were randomly selected from 210 eligible survivors and invited to participate
10 survivors refused participation
117 family doctors of the 123 survivors invited
2 family doctors refused*
115 family doctors entered the study
121 survivors entered the study
6 survivors dropped out
115 survivors were assessed by their family doctor in second year
100 survivors received follow-up advice at the LTFU clinic
15 survivors received follow-up advice by telephone

Figure 1: Trial profile

of these two doctors were invited separately by the LTFU clinic, but did not enter this study). In total, 12 of 133 invited survivors did not participate in the study, therefore, 121 survivors entered this study. Table 1 shows characteristics of all 133 individuals. Survivors completed HRQoL assessments by use of RAND-36 subscales. Table 2 shows the outcomes of the RAND-36 subscales for the study group, and the mean scores from the available Dutch reference group. Survivors showed significantly lower HRQoL scores compared with the control group on the subscales for physical functioning (p=0·011), social functioning (p=0·027), vitality (p=0·005), and general-health perceptions (p<0·0001).

Table 1: Demographic and clinical data of participating adult survivors and non-participants

	Participants (n = 121)	Non-participants (n = 12)
Patient characteristics		
Median age at study, years (range)	34 (19-60)	28 (19 – 49)
Median age at diagnosis, years (range)	6 (0-38)	4 (1 -18)
Median time since diagnosis, years (range)	27 (9-38)	25 (18 – 31)
Male (n)	64	7
Initial diagnosis (n)		
Leukaemia	53	3
Malignant lymphoma	20	1
Bone sarcoma	23	3
Soft- tissue sarcoma	6	1
Wilms'tumour	4	0
Langerhans-cell histiocytosis	8	2
Other	7	2
Treatment (n)		
Chemotherapy only	48	9
Radiotherapy only	5	0

Table 2: Means and SDs for RAND-36 subscales, in survivors and in Dutch controls (aged 25-44 years) at visit 1

	Study group(n=121)	Controls (n = 416)	
Physical functioning	84.9 (20.0)	89.7 (16.3)	p=0.011
Social functioning	85.4 (18.9)	89.4 (17.0)	p=0.027
Role limitations due physical problems	80.7 (31.8)	82.7 (32.2)	p=0.0500
Role limitations due to emotional problems	86.6 (30.3)	84.6 (31.5)	p=0.472
Mental health	77.6 (16.1)	77.9 (17.7)	p=0.853
Vitality	62.9 (20.1)	68.2 (18.9)	p=0.005
Bodily pain	83.5 (19.2)	84.0 (22.9)	p=0.787
General health perceptions	67.4 (21.7)	75.9 (20.2)	p<0.0001

At visit 2, 115 of 121 (95%) survivors were assessed by local family doctors. Of the six survivors who were not assessed, two survivors had left the country, two survivors were starting treatment with growth-hormones and therefore did not have time to visit their local family doctor, and two survivors decided to end follow-up because they did not want to be reminded of their cancer (figure). Completed forms for medical history and physical assessment were returned by 103 of 115 (90%) local family doctors, and two (2%) local

Table 3: Patient satisfaction with shared-care follow- up according to Likert scale

	Patients n (%)
Satisfied with the care given by doctor	
Very satisfied or satisfied	89 (88)
Neutral	6 (6)
Not satisfied	5 (5)
Satisfied with time available during screening by doctor	
Very satisfied or satisfied	88 (87)
Neutral	3 (3)
Not satisfied	8 (8)
Satisfied with doctor's knowledge of my medical history	
Very satisfied or satisfied	78 (77)
Neutral	8 (8)
Not satisfied	14 (14)
Doctor's attitude was friendly	
Very satisfied or satisfied	94 (93)
Neutral	2 (2)
Not satisfied	3 (3)
Satisfied with answers given by doctor	
Very satisfied or satisfied	85 (84)
Neutral	7 (7)
Not satisfied	8 (8)
Satisfied with the booklet, summary of diagnosis and treatment (n=121*)	106 (88)
Very satisfied or satisfied	13 (11)
Neutral	2 (2)
Not satisfied	
Before being recalled to follow-up, I was already informed about possible late toxic effects (n=121*)	
Yes	36 (30)
No	85 (70)

Data are for 101 of 115(88%) patients who completed questionnaires. * All 121 patients who entered the study were able to answer this question. Percentages might not add to 100% due to rounding.

family doctors reported findings of their assessments by telephone because their patients had forgotten to take the forms with them to visit 2. Complete data, including those for laboratory tests, radiographs, and echocardiograms were received by the LTFU clinic from 98 of 115 (85%) local family doctors.

The seven-item satisfaction questionnaire was completed by 101 of 115 (88%) survivors (table 3). 89 of these 101 (88%) survivors were satisfied with the care given by the local family doctors at visit 2.

14 of the 101 (14%) survivors thought that their local family doctor's knowledge of their medical history was inadequate. The most frequent remarks for these patients were: "I

had the feeling that the family doctor did not know what he/she was expected to do" (seven of 101 [7%] survivors), "there was too little time to perform the investigations" (five of 101 [5%] survivors), and, "I had the feeling the family doctor was reluctant to perform the investigation" (three of 101 [3%] survivors).

Data from the three-item questionnaire for local family doctors showed that 94 of the 115 (82%) participating local family doctors were satisfied with this shared-care collaboration and thought the information they had received from the LTFU clinic was adequate, 18 of 115 (16%) local family doctors had no opinion, and three of 115 (3%) local family doctors were dissatisfied.

Before visit 1, 85 of the 121 (70%) survivors had not received information about the possibility of late effects. At visit 1, 64 of 121 (53%) survivors had mild late effects (grade 1 or 2) and 48 of 121 (40%) survivors had moderate-to-severe late effects (grade 3 or 4); additionally 85 of 121 (70%) survivors had two or more late effects and 37 of 121 (31%) survivors were diagnosed with previously unknown grade 2–4 late effects that needed treatment or closer monitoring. The most commonly recorded late effects were cosmetic, eg, amputations, scars from surgery, asymmetric body growth due to radiation damage (35 of 121 [29%]), orthopaedic (24 of 121 [20%]), endocrine deficiencies (20 of 121 [17%]), infertility (19 of 121 [16%]), cardiac damage (11 of 121 [9%]), and second malignant tumour (11 of 121 [9%]). Five survivors had a second malignant tumour (one meningioma, one oesophageal carcinoma, and three basocellular carcinomas) that had not been diagnosed before.

At visit 3, 100 patients received advice at the LTFU clinic and 15 patients received advice by telephone. RAND-36 was completed by 110 of 115 (96%) survivors (data not shown). No significant differences in any of the subscales were noted between visit 1 and visit 3. More detailed information about late effects and HRQoL of almost the same study group has been published in an earlier study in which 117 of 121 (97%) survivors of our current study.[19]

DISCUSSION

123 of 133 (92%) invited survivors and 115 of 117 (98%) family doctors agreed to take part in the shared-care programme. Since 89 of 101 (88%) survivors who completed satisfaction questionnaires and 94 of 115 (82%) family doctors were satisfied with the programme, our findings have shown that shared-care by paediatric oncologists and family doctors is feasible for long-term follow-up of adult survivors of childhood cancers.

Collection of long-term follow-up data for registration purposes of late effects is acceptable. However, improvement of the exchange of information between family doctors and the LTFU clinic remains a challenge. Shared electronic health records, including information

about diagnosis, treatment, and future screening practices, might be helpful.[20] In our earlier study,[9] 110 of 233 (47%) family doctors preferred communication by email or by use of a website to submit forms. In the same study, most family doctors were willing to participate in long-term follow-up of adult survivors of childhood cancers, on the condition that guidelines and adequate medical information were provided and that there was one contact person at the LTFU clinic. The family doctors in that study were a different group to that in the present study; although, there was an overlap of 13 family doctors between both studies. Models of shared care have been developed for chronic diseases such as diabetes, hypertension, and asthma,[21,22] and there are some examples of shared oncological care for adult patients with cancer.[23,24] Some studies suggest that family doctors are willing to take part in follow-up care of patients with cancer,[9,25] and that hospital follow-up provides no advantages compared with long-term follow-up in primary-care settings.[22,24] "Developing personal relationships", "gaining mutual respect", and "increasing medical knowledge for the benefit of their patients", seemed to be the most important motivational factors to persuade family doctors to collaborate with specialist services.[26] For shared-care models to be successful, family doctors need to view such programmes as an improvement from usual care in general practice, rather than as a downgrade from hospital practice.[27]

In our current study, most (85 of 121 [70%]) of the survivors who were recalled had not received information about the possibility of late effects from treatment before their visit, and consequently, were at risk of delayed medical care if health problems were to occur. Therefore, survivors should be fully informed and family doctors should know about the possible late effects of cancer treatment and their effects on health; participation in a shared-care programme should help update family doctors' knowledge. In our study, all family doctors were given information on their patients' history, health risks, and required tests. But 14 of 101 (14%) survivors were dissatisfied with their family doctors' knowledge about their medical history. Improvement of family doctors' knowledge about late effects is important because this is important for survivors of childhood cancers.[28] Training in survivorship care should be incorporated into training programmes for family doctors.

At present, not all long-term survivors are in long-term follow-up, and as age increases, the likelihood of receiving adequate long-term follow-up decreases.[7] Furthermore, whereas the incidence of many modifiable late effects of treatment increases with age, the likelihood of receiving cancer-related care decreases with time. Many cancer survivors are discharged years before follow-up, and some services still discharge survivors as soon as they reach adulthood.

Survivors sometimes view hospital-based follow-up as problematic as they reach adulthood. Loss of long-term cancer survivors to follow-up should be avoided because many of the potentially serious late effects might not manifest until decades after completion of

treatment. Oeffinger and co-workers[29] reported that patients diagnosed with malignancy between 1970 and 1986 and who had subsequently survived cancer, showed increased vulnerability to diseases associated with ageing, such as second cancers, cardiovascular disease, renal disease, musculoskeletal disorders, osteoporosis, and infertility, compared with their siblings.[29] Therefore, adult survivors of childhood cancers should be recalled for follow-up.

In our study, a substantial proportion (48 of 121 [40%]) of adult survivors had moderate-to-severe late effects. In another study,[19] such survivors had significantly lower quality of life compared with survivors who had no or only mild late effects. In the current study, 37 of 121 (31%) survivors had previously undetected late effects that needed treatment or closer monitoring. Therefore, the recall of these survivors was worthwhile for managing the late effects and for minimising morbidity and the risk of severe complications. The long-term costs of early identification and treatment of late effects need further study. Although we did not undertake a cost analysis, shared care probably costs less than follow-up in a LTFU clinic alone. As the number of cancer survivors is increasing, the time has come to identify new models of cost-effective long-term follow-up.

Up to now, long-term follow-up of childhood-cancer survivors has been mainly organised by paediatric oncologists, and family doctors have rarely been involved. Yet, paediatric oncologists are ill-equipped to assess adult patients. Highlighting the need for new approaches to long-term care, Goldsby and colleagues[30] suggested four possible models—those driven by patients, family doctors, paediatric oncologists, or adult medicine health-care workers. Each model has its advantages and disadvantages, and more than one model might be needed.[31] Since childhood-cancer survivors are a very heterogeneous group, Wallace and co-workers[18] suggested that follow-up should be organised into three levels according to a patient's individual risk profile.

Clear advantages of follow-up care given by local family doctors rather than by hospital staff include less patient travel, shorter waiting times, better patient familiarity with surroundings (ie, the doctor's practice), and less stigmatisation. As survivors grow older and possibly develop additional chronic illnesses of age, access to care in the context of total health needs is more useful.

In the past 10 years, studies have begun to document late effects of treatment in survivors of adult cancers.[32-34] Care for these survivors, provided by oncologists, generally does not extend beyond surveillance for recurrence of the cancer, and after about 5–10 years, patients are discharged without specific plans for monitoring.

Busy oncology practices, which focus on patients undergoing active treatment, are not appropriate for life-long follow-up of cancer survivors. Collaboration with family doctors in a shared-care model might provide a solution. A few studies[23,24] have suggested that such a model is applicable to the care of adult cancer survivors. Given predictions that 300

million people will be diagnosed with cancer over the next 15 years, and over one-third of these will become cancer survivors,[35] collaborative shared care between specialists and family doctors is needed.

Our study has some limitations. We did not use predefined criteria to establish whether our model would be successful enough to progress to the next phase of a large study. However, we think there is no standard of what would be an acceptable amount of participation, satisfaction, or return of requested data.

Since we only recalled survivors who were not receiving any kind of follow-up, we could not compare our model to others. More studies are needed to assess whether a shared-care approach results in an equitable standard of care for survivors. Family doctors already have the skills to screen patients at increased risk of developing health problems such as diabetes and cardiovascular disease. With easy ways to communicate with LTFU clinics and the availability of guidelines, they should also be able to screen adult survivors of childhood cancer. We wish to emphasise that the success of a shared-care model depends on a key coordinator, who could be an academic family doctor with an interest in late effects (as used in this study), a nurse practitioner, or a dedicated nurse.

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CHAPTER 8

Discussion & Future Perspectives

INTRODUCTION

The general aims of the thesis are

1. To investigate late effects in adult survivors of childhood cancer.
2. To study a shared-care model for the long-term follow-up of adult survivors of childhood cancer where the paediatric oncologist and the patient's own general practitioner collaborate.

In the first part of this final chapter, some overall conclusions about the two primary research aims are discussed. The chapter will end with a discussion of the findings for future practice and recommendations.

Improved survival in childhood cancer patients is a fantastic achievement of modern medicine. However, along with improved survival has come the recognition of the many long-term effects of cancer and its treatment. Childhood cancer survivors are vulnerable to health problems which may not become apparent until years after therapy. Adverse late effects secondary to previous treatment of childhood cancer with chemotherapy or radiation are common. As many as two-thirds of survivors of childhood cancer will experience a late effect.[1-4] Some health care providers believe that many childhood cancer survivors will do well and they emphasize that long-term follow-up for these patients might have negative consequences. Together with the fact that the cost of routine follow-up for all survivors will be considerable makes that they are in favour of a patient driven model for follow-up. They suggest that the survivor is given a summary of therapy and is educated regarding risks, and seeks care if necessary. In Chapter 2 we showed that childhood cancer survivors with a follow-up of more than 20 years have significantly lower quality of life as assessed by lower scores on the RAND-36 physical functioning, vitality, bodily pain and general health perception subscales, and have significantly more severe late effects than those with a follow-up of less than 20 years. In Chapter 3 we showed that 39% of the participating survivors had severe late effects (grades 3–4) and that these long-term complications were not always recognized by survivors and health care providers.[5] Over time, childhood cancer survivors become less likely to return to their initial cancer centre for follow-up and frequently lack detailed knowledge of their prior treatment.[6,7] This thesis has shown that it is worthwhile recalling older adult survivors to follow-up care.

Risk-based follow-up can provide for early detection and sometimes intervention, and can help reduce cancer-related morbidity and mortality. There is consensus that a plan for follow-up should be available for all survivors of childhood cancer.[8] However, it is unclear where and by whom this follow-up should be organized.

Since the number of survivors of childhood cancer is increasing and hospital-based lifelong follow-up will not only be difficult to organize but also very expensive, we have

to look for alternative follow-up programmes offering the lowest burden, not only on the survivors but also on the expanding health care budgets in many Western countries. GPs present a good possible alternative, since GPs are generalists and easily accessible.

Present conditions

The majority of existing follow-up programmes are organized in paediatric institutions, without significant input from adult-oriented, generalist health care providers. A survey in the USA in 1998 revealed that around one-half of all member institutions of the Children's Cancer Group (CCG) and the Paediatric Oncology Group (POG) have a long-term follow-up clinic and mechanisms for following adult survivors, but only 15% have established a database for adults.[9] An adult oncologist was involved in only 13% of these programmes, a general practitioner (GP) in only 8%. In 2005 we distributed a similar survey to 394 hospitals who were members of the Children's Oncology Group (COG); Stichting Kinderoncologie Nederland (SKION); Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH); and the Nordic Society for Pediatric Hematology and Oncology (NOPHO)(data unpublished). Although the response was low (119/394, 30%) the conclusions were comparable with the earlier survey done by Oeffinger. Almost 66% of the institutions had some kind of follow-up for adult survivors of childhood cancers. Some patients were seen at the LTFU clinic, but follow-up was also done by telephone interviews or by sending questionnaires by post. In those institutions where adult survivors were seen at follow-up, the screening was performed in 60% of the cases by paediatric oncologists, in 14% by an adult oncologist or internist, and a GP was involved in only 6% of cases. In the Netherlands three of the six LTFU clinics had adult specialists involved in the follow-up care of adult survivors but the involvement of GPs was rare.

Of course it is important for paediatric oncologists to continue registration of late effects. Paediatric oncologists have instituted a variety of refinements designed to minimize long-term complications, including changes in dosage and schedules for radiotherapy, enhanced monitoring during treatment, with modification to chemotherapy dose, research into less toxic agents, and reduced use of prophylactic cranial radiation therapy.[10] The combined efforts of paediatric oncologists and physicians for adults will be required to observe, describe and report the consequences of newer agents and combinations. In this way future generations of doctors will be able to assess the impact of these treatments on the long-term quality of life.

Up to now, long-term follow-up of childhood-cancer survivors has mainly been organised by paediatric oncologists, and GPs have rarely been involved. Yet, paediatric oncologists are ill- equipped to assess adult patients and with the ever enlarging population of adult childhood cancer survivors time has come to identify new models of cost-effective long-term follow-up.

Shared care

With the increasing number of adult survivors of childhood cancer, physicians for adults – i.e. internists, cardiologists, endocrinologists, neurologists and GPs – will increasingly meet these patients. An understanding of the late effects of cancer therapy is important for all doctors, generalists and specialists, adult and paediatric, to supply the best care for the growing population of adult survivors of childhood cancer.

GPs and specialists are accustomed to working together in the management of complex health conditions. For example, GPs work with specialists in coronary artery disease, heart failure, diabetes, chronic renal insufficiency, bipolar disorder, Parkinson's disease and inflammatory bowel disease. A similar working relationship could be established to care for cancer survivors. It is also important to realize that the aim is to diagnose late effects of cancer treatment and not to treat late effects. GPs already have the skills to screen patients at increased risk of developing health problems such as diabetes and cardiovascular disease. With the appropriate guidelines available, the assessment of late effects can be undertaken by the GP. If serious late effects such as cardiac or endocrine complications are detected, survivors can be referred to an appropriate consultant.

"Shared-care", in which GPs collaborate with cancer specialists, could offer a solution to ensure the delivery of quality survivorship care. Under the shared-care model, both the GP and the cancer specialist pool their resources and talents to offer quality care. For shared-care to become successful, several challenges must be overcome. In engaging GPs in survivorship care it is important to remember that effective strategies tend to work from the bottom up, not from the top down.[11] It is important that GPs and cancer specialists reach a common understanding of the expected components of care and their respective roles. This understanding requires specialists to acquire greater confidence in the ability of GPs to deliver care. If a paediatrician has little confidence in the knowledge, skills or flexibility of a GP, he or she will have difficulties in handing over the patient.[12] This results in paediatricians continuing to see patients well into adult life, because paediatricians see themselves as the best caregivers regardless of the patient's age.

Clear advantages of follow-up care delivered by the local GP include less patient travel, shorter waiting times, and patient familiarity with the surroundings and less stigmatization. GPs are better qualified to ensure that the full spectrum of the cancer survivors' health needs is addressed, not only issues concerning the cancer but also primary and secondary prevention, the management of concurrent co-morbid disease (e.g. heart disease or diabetes), mental health and acute care. GPs face challenges in delivering survivorship care. The fact that the patient was previously diagnosed with cancer may itself be unknown to the GP, and even when this history is obtained, records of the specific diagnosis and

treatment may be unavailable or practice guidelines on recommended follow-up lacking. Arguments often heard against involving GPs in long-term follow-up are that GPs only have a few of these survivors in their practice, that GPs lack knowledge of the late effects of cancer treatment, and that by involving GPs the care becomes far too diverse. However, GPs will increasingly have to handle the late effects of cancer treatment because the survival of childhood cancer has improved and there are increasingly many young adults who have survived adult cancers (e.g. testis cancer, breast cancer, malignant lymphoma, colon cancer) and who are at risk of late effects. Lack of knowledge is a serious problem. GPs will hesitate when asked to get involved in long-term follow-up care, which will also be a reason for survivors to prefer being followed by the doctor who treated them in the past. It is no wonder that GPs lack knowledge about late effects if they are not informed during their studies and information about late effects is rarely published in journals for GPs. Seminars and conferences about late effects are mainly organized for paediatric oncologists, internists and endocrinologists, but GPs are rarely invited. Most GPs do not receive an end of summary or guidelines for future follow-up. However, when a health problem occurs in survivors of childhood cancer, most patients will consult their GP first, who could underestimate the problem if he or she is unaware of the possibility of late effects.

Survivorship care plan

As GPs are involved in the long-term follow-up care of survivors of childhood cancer or survivors of adult cancers, it is important to supply a survivorship aftercare plan for every survivor cured. The survivorship aftercare plan is a document created by those primarily responsible for the cancer treatment to provide detailed information regarding patient's cancer and treatment history, guidelines for future follow-up and advice about a healthy lifestyle, and it must indicate by whom and in what setting follow-up care is provided. The purpose of a survivorship care plan is to serve as a vehicle of communication between the survivors and their health care providers. Plans should not be static but tailor-made. They might change over time in response to the aging of the survivor or to new knowledge about late effects or recommendations for further monitoring. Electronic medical records will be helpful for regular updating of this plan. Survivors, oncologists and GPs generally agree that cancer patients would benefit greatly if a survivorship aftercare plan was provided to them and their health care providers.[13] GPs would benefit because they could assess their patients with a history of cancer without having to wade through multiple letters from oncology providers. GPs were so enthusiastic at such a survivorship aftercare plan being made available to them that many suggested that, all other things being equal, they would refer patients to oncology providers who distributed this aftercare plan instead of to those who did not. The majority of oncology providers interviewed in the

same study recognized the potential benefit but were unwilling to provide this summary because they would receive no time-saving or monetary benefit as a result of doing so.[13] The lack of such a comprehensive plan outlining the specific needs of cancer survivors could contribute to the incomplete transition of care from cancer specialist to the GP, resulting in the loss of the opportunity to transfer essential information. Such a plan could facilitate GPs in providing high quality and necessary follow-up care.

Future perspectives and recommendations

Recently, more information has become available about the adverse late effects after treatment of adult cancer. Because childhood is a time of rapid physical growth and emotional development, the consequences of therapy can be different from the results of similarly treated adults. However, there are also late effects comparable to those we know from childhood cancer, for instance the cardiovascular risk after treatment with anthracyclines or radiation. Care provided to these adult survivors by an oncologist generally does not extend beyond monitoring for recurrence of the cancer, and after a variable period of about 5–10 years patients are discharged without a plan for monitoring. A busy oncology practice, with a focus on patients undergoing active treatment, is not appropriate for the lifelong follow-up of all survivors of cancer. Collaboration with GPs could also provide a solution for the long-term follow-up of adult cancer survivors. Given the prediction that 300 million people will be diagnosed with cancer over the next 15 years, and over one-third of these will become cancer survivors[14], collaborative shared-care between specialists and GPs is required. Recently, the Health Council of the Netherlands published a report calling for a systematic approach to aftercare in the following five years and according to guidelines that have yet to be developed.[15]

Survivorship care needs to be tailored to the patient's clinical state and preferences. Survivors of childhood cancer are a heterogeneous group with heterogeneous health problems, which is why they do not fit within a single medical specialization. Late effects of childhood and adolescent cancer treatment display great diversity and can be life threatening, disabling or mild and just inconvenient. The severity of the risk for late effects depends on the former diagnosis and treatment. Fortunately, not all survivors will encounter severe health problems. Some patients are cured with surgery, have few long-term effects, and want to move on with their lives. Others may have severe late effects and need close monitoring by specialists from a LTFU clinic. Survivors who are doing well will be reluctant to continuously return to a tertiary centre for routine visits for psychological, cost or time-related reasons. Without the information from unaffected survivors, there is a risk of overestimating adverse outcomes. It is also important that survivors at a low risk of health problems are not stigmatized by keeping them unnecessarily in follow-up at a tertiary centre. We believe that risk-based follow-up as suggested by Wallace et al. could offer a solution for the follow-up care of the ever-increasing cohort of childhood

cancer survivors. Wallace suggested organizing follow-up on three levels, according to the individual risk profile of survivors.[16] Patients with no or very low risks (surgery only, no radiation and chemotherapy not including an alkylating agent, anthracycline, bleomycin or epipodophyllotoxine) could be followed by questionnaires or telephone follow-up. The local GP could play a role in the follow-up of the medium-risk group (no radiation or low or moderate dose alkylating agent, anthracycline, bleomycin or epipodophyllotoxine). For childhood cancer survivors with complex medical needs (stem cell transplant, any amount of radiation, or high dose alkylating agent, anthracycline, bleomycin or epipodophyllotoxine) a multidisciplinary model of care as described by Carlson would be ideal.[17] This model provides same-day, same clinic access to oncology/survivorship care, as well as care in the areas of endocrinology, pulmonology, cardiology, nutrition and psychology. This kind of clinic should also be open to young adults with complex health needs who were treated in adult settings for testis carcinoma, Hodgkin's or Non-Hodgkin's disease, mamma carcinoma or colon carcinoma, for instance. Organizing risk-based follow-up according to this three-level model would allow LTFU clinics to concentrate on the survivors with the highest health risk. Furthermore, the ongoing communication between the LTFU clinic and the GP will improve the GP's knowledge of late effects. Medical education programmes for GPs must be available to improve survivorship care competency. GPs must be conscious of their limitations and engage specialist consultants if they need help. Both parties should agree on what needs to be done and who will do it.

This thesis has shown that shared-care is feasible but more randomized clinical trials are needed to test different approaches to deliver shared-care.

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CHAPTER 9

Summary

Summary

Since the sixties the survival rate for children with cancer has increased from less than 25% till around 75% nowadays.

The increase in survivability of childhood cancer has translated into a growing population of young adult survivors. At the same time it has become clear that the success of cure has not come without cost. Studies estimate that at least two-thirds of adults who survived childhood cancer have had at least one late complication and approximately one-third have had serious or life-threatening complications.

Childhood cancer survivors have an excess risk of mortality due to relapse of the primary cancer or therapy-related secondary cancers and late complications, mainly cardiac or pulmonary disease. For a long time, it was common practice to discharge paediatric cancer patients after a disease-free interval of approximately ten years. Young children continued follow-up until they reached adulthood about the age of 18 years.

To reduce the morbidity of late effects it is important to detect and treat diseases as early as possible, preferably at a subclinical stage. The scope of late effects has not yet fully been mapped, as the oldest survivors are now between the ages of 30 and 40, and we do not yet know the health risks of the elderly. Therefore, follow-up should be combined with reliable registration and research on late complications and risk factors. For this purpose, survivors of childhood cancer need periodic assessments and information about the health risks, together with lifestyle counselling (for example regarding smoking, alcohol and exercise) to decrease further damage.

Nowadays paediatric oncologists world-wide believe that a systematic plan for lifelong screening and surveillance should be offered to all survivors. At present not all adult survivors of childhood cancer get the necessary follow-up. Based upon the assumption that follow-up is required and important, the question arises as to who is best suited to provide this care and where is the best place for follow-up. This thesis deals with the role the general practitioner could play in the long-term follow-up of adult survivors of childhood cancer.

Chapter 1 gives a general overview of the reasons for long-term follow-up, different models for follow-up and the present situation in the Netherlands.

In the study described in **Chapter 2**, we assessed health-related quality of life (HRQoL) of adult long term (up to 20 years) and very long term (over 20 years) childhood cancer survivors, compared to the HRQoL of an age matched Dutch population sample. Also we evaluated the impact of cancer related adverse late effects on the functional, psychological and social health of childhood cancer survivors. To assess HRQoL in all adult (age 18 years and older) survivors who had attended the long-term follow-up clinic since 1995 we used the RAND-36. This is an internationally used validated and reliable generic self-report questionnaire to assess HRQoL, containing eight subscales. The survivors were

divided into two groups based on the length of follow-up: Group LF (long term follow-up, follow-up up to 20 years, n=129) and Group VLF (very long-term follow-up, follow-up over 20 years, n=184). Data on diagnosis, treatment and complications were obtained from medical records. Late effects were graded using the Common Terminology Criteria for Adverse Events, version 3 (CTCAEv3). Except for higher scores on the subscale Bodily pain, LF patients did not differ significantly on the RAND-36 subscales from the population sample; VLF patients had significantly lower scores on the subscales physical functioning (P=0.003), social functioning, vitality and general health perception (P<0.001). Significantly more VLF patients (P<0.001) had severe (grade 3 and 4) late effects (47.8%) compared to LF patients (27.9%). Female gender and especially psycho-social late effects were inversely related to HRQoL. Childhood cancer survivors who were diagnosed more than 20 years ago had lower scores on the RAND 36, and had significantly more severe late effects than those diagnosed more recently. These findings also suggest that there is no plateau in the occurrence of late effects although longitudinal studies are needed to confirm this.
In **Chapter 3** we assessed health status and health related quality of life (HRQoL) in 123 childhood cancer survivors, median age 33 (19-50) years, follow-up 27 (9-38) years, who were recalled to the long-term follow-up clinic and were not yet involved in regular long-term follow-up. HRQoL data were compared to an age-matched control group from the Dutch population. Grade 1-2 late effects were found in 54% of the survivors, grade 3-4 in 39%, two or more late effects in 70%, and grade 2-4 previously unknown late effects in 33%. Survivors had significantly lower scores on the subscales physical functioning, social functioning, vitality and general health perception of the RAND-36 compared to controls. Survivors who had no late effects or only mild late effects had significantly better scores on most of the RAND-subscales compared to survivors with severe late effects. We concluded that as nearly 40% of these long-term childhood cancer survivors suffer from moderate to severe late effects and 33% had previously unknown late effects it is worthwhile to recall these patients to follow-up.
In **Chapter 4** we assessed knowledge of disease, treatment and potential late effects in adult survivors. Between 2004 and 2006 all 195 adult survivors visiting the long-term follow-up clinic (LTFU) were asked to complete a ten-item questionnaire on knowledge of disease, treatment and late effects. Survivors were divided into group Recalled (survivors who were newly recalled to follow-up) and group Regular (survivors who were already seen in regular follow-up). Total knowledge score (TKS) was calculated as a percentage of the maximum possible number of correct answers. Questionnaires were completed by 186/195 (95.4%) survivors. One hundred sixty seven of the 186 survivors who completed the questionnaire (89.8%) knew the name of the cancer, 107/186 (57.5%) knew the precise diagnosis. Of those who knew they received radiotherapy 77/107 (71.9%) knew the exact radiation field; of those who knew they underwent surgery 60/80 (75.0%)

knew the detailed procedure, of those who had chemotherapy only 2 survivors knew the chemotherapeutic agents. TKS score in group Regular was higher than in group Recalled (83.3% versus 71.4%; p=0.026). Group Regular survivors were more aware of potential late effects than group Recalled survivors (p=0.004). TKS was positively correlated with being aware of potential late effects (p<0.0005).

Survivors participating in regular follow-up had higher TKS and were more aware of potential late effects than first-time visitors. Although survivors in regular follow-up have better knowledge compared to those who were not in regular follow-up they still have some noteworthy knowledge deficits.

In **Chapter 5** we investigated the results of a simple home- based counselling physical activity program with feedback of a pedometer on adult childhood cancer survivors with fatigue.

Fatigue may occur long after the end of treatment of childhood cancer and has negative effects on quality of life. Current revalidation programs which include physical activity stimulation, are of benefit, but are intensive and time consuming, which makes them less suitable for young survivors of childhood cancer who often stand at the beginning of a professional career or have a family. Adult survivors of childhood cancer were recruited from the LTFU clinic of the UMC Groningen, the Netherlands. A score of 75mm on a Visual Analogue Scale (VAS)(score 0-100 mm) for fatigue was used as an inclusion criterion. Seventy-six subjects were eligible; 21 did not want to participate, 46 entered the study and 8 dropped out during the study. There was a control group of age matched healthy siblings or friends (n=33). A counsellor advised the participants how to increase their daily activity. Fatigue was the primary outcome and was measured with the Checklist Individual Strength (CIS) at the start of the program (T0), after 10 weeks (T10) and after 36 weeks (T36) in participants as well as controls. Registration of the daily number of steps using a pedometer was done at an (online) step dairy at start and after 4 and 10 weeks. The mean CIS score of the participants significantly improved after the intervention (T10) and this improvement held at least till 36 weeks. The participants showed also a significant increase in daily steps (p<0.001) after the intervention (T10). The CIS scores of the controls didn't change significantly during the study. We concluded that physical activity stimulation using counselling and a pedometer during 9 weeks leads to a significant improvement of fatigue in adult childhood cancer survivors with fatigue, lasting for at least 36 weeks.

In **Chapter 6** we investigated the willingness of GPs, who had followed a postgraduate course on late effects of cancer treatment, to participate in a shared care model for follow-up of adult childhood cancer survivors, as well as what their requirements would be in case of participation.

Long-term follow-up of childhood cancer survivors is mainly organised by paediatric oncologists and until now general practitioners (GPs) are rarely involved. To ensure

appropriate follow-up for all survivors into adulthood, a combined effort of paediatric oncologists and general practitioners might be the solution. From the Northern Netherlands 358 GPs participated in a postgraduate course on late effects in paediatric cancer survivors. After the course they were asked to complete a 10-item questionnaire on motivation to participate in the regular follow-up of adult childhood cancer survivors as well as their conditions to participate. The response rate was 65%. Of the responders 97% were willing to participate in a shared care model for follow-up and 64% felt that it belonged to their responsibility to be in charge of childhood cancer survivors. The main requirements for participation were the availability of guidelines (64%), sufficient information about the patient's medical history (37%) and short communication lines (45%). The main barriers to participate were workload (16%), lack of knowledge (15%) and lack of communication (13%). We concluded that a significant number of GPs are ready to participate in the long-term follow-up of adult childhood cancer survivors if adequate guidelines and medical information is provided and communication lines are clear. About 64% (150/233) of the GPs thought that participating would be a normal part of the care that GPs should provide.

In **Chapter 7** we described a 3-year study to assess whether shared-care by paediatric oncologists and family doctors in the long-term follow-up of survivors of childhood cancer is feasible, whether a shared-care model is compatible with collection of data needed for registration of late effects, and how a shared-care model is assessed by survivors and family doctors.

We explored a shared care model in which the paediatric oncologist cooperates with the local GP while a GP working at the LTFU clinic is coordinating the follow-up from both a research and clinical perspective.

The local GP was informed about the possible health risks of his/her patient and the individual guideline was provided before the survivor visited his/her GP. The GP was requested to return information of the screening and the required tests to the LTFU clinic. One hundred and twenty three survivors of childhood cancer entered the study. Patients made two visits to the LTFU clinic interspersed with a visit to a local family doctor dedicated to the discussion of their cancer treatment. One hundred and twenty three of 133 (92%) eligible survivors, and 115 of 117 (98%) of their family doctors agreed to participate in the shared-care programme. One hundred and three of 115 (90%) family doctors returned data to the LTFU clinic. Satisfaction of patients and doctors with the family-doctor consultation was assessed at the end of the study. Eighty-nine of 101 (89%) patients who completed the study were satisfied with the shared care, as were 94 of the 115 (82%) family doctors.

In the general discussion **Chapter 8** we discussed the present models for long-term follow-up. We reviewed questions and controversies concerning the role of the GP in the

long-term follow-up care and made some recommendations for the future. We concluded that a shared care model is feasible for long-term follow-up of adult survivors of childhood cancer.

We feel that follow-up care should be tailor- made and therefore more than one model for follow-up of childhood cancer survivors will be needed. Models must be flexible and be sensitive to change throughout the life cycle; young children have different needs than young and older adults. Follow-up should be based on the individual risk of late effects as described by Wallace and for those who are at little or no risk alternative forms of follow-up as questionnaires or telephone interviews should be considered. Survivors' own views on follow-up care should be taken into account as well and these views may change as survivors grow into adulthood. Only then one can avoid losing long-term survivors of childhood cancer as they grow-up, which is important as many of the potentially serious late effects may not manifest until a decade after completion of treatment or later.

CHAPTER 10

Nederlandse samenvatting

Samenvatting

Sinds de jaren zestig van de vorige eeuw zijn de overlevingskansen van kinderen met kanker gestegen van destijds minder dan 25% tot nu ongeveer 75%. Tegelijkertijd wordt echter duidelijk dat de behandeling, die zo succesvol is om de kanker te bestrijden, zijn tol eist in de vorm van blijvende gevolgen. Tenminste tweederde van de volwassenen die als kind voor kanker zijn behandeld krijgt te maken met late effecten van behandeling, die vaak irreversibel zijn, veelal behandeling behoeven en die in ernst variëren van mild tot ernstig of soms zelfs levensbedreigend. De sterftekans voor deze patiënten blijkt significant hoger te zijn dan voor leeftijdgenoten.

In de kinderoncologie was het gedurende lange tijd gebruikelijk patiënten uit controles te ontslaan na een ziektevrije periode van 10 jaar. Jonge kinderen bleven meestal voor controle komen tot de voltooiing van hun lichamelijke groei; in de praktijk was dit vaak tot het 18de levensjaar. Om de morbiditeit van later optredende complicaties zoveel mogelijk te beperken is het echter van belang behandelbare aandoeningen in een vroeg, liefst subklinisch stadium, te diagnosticeren. Omdat het terrein van de late effecten nog maar ten dele in kaart is gebracht – immers de "oudste" overlevenden zijn gediagnosticeerd in de jaren zeventig van de vorige eeuw en hebben nu een leeftijd tussen de 30 en 40 jaar; over de gezondheidsrisico's op hogere leeftijd is nog weinig bekend - dient deze follow-up gekoppeld te worden aan betrouwbare registratie van gegevens en aan onderzoek naar nog onbekende complicaties en risicofactoren. Ten behoeve hiervan zullen de patiënten periodiek moeten worden onderzocht. Daarnaast is het nodig hen goed te informeren over de gezondheidsrisico's die zij lopen als gevolg van hun vroegere behandeling, waarbij ook leefstijladviezen (roken, alcohol, lichaamsbeweging, voeding) aan de orde moeten komen.

Tegenwoordig is het de aanbeveling van kinderoncologen over de hele wereld om de noodzakelijke controles zeer langdurig cq levenslang voort te zetten. Toch blijkt dat lang niet alle overlevenden van kinderkanker op deze wijze gevolgd worden. Er van uitgaande dat follow-up nodig en nuttig is, rijst de vraag hoe vaak, op welke manier, waar en door wie deze controles moeten worden uitgevoerd. Dit proefschrift onderzoekt of de huisarts een rol kan spelen in deze noodzakelijke lange termijn follow-up.

Hoofdstuk 1 geeft een overzicht van de verschillende redenen voor follow-up, de verschillende modellen en de huidige situatie in Nederland. In de studie die beschreven wordt in **Hoofdstuk 2** wordt de Health Related Quality of Life (HRQoL) van volwassen overlevenden van kinderkanker die korter dan 20 jaar geleden zijn behandeld vergeleken met overlevenden die langer dan 20 jaar geleden zijn behandeld. Ook wordt de HRQoL van beide groepen vergeleken met een steekproef uit de algemene populatie. Verder hebben we de invloed van de late effecten van de behandeling voor kinderkanker nagegaan op het lichamelijk, geestelijk en sociaal welbevinden van de overlevenden. Voor het vastleggen

van de HRQoL van alle overlevenden ouder dan 18 jaar die sinds 1995 een bezoek hadden gebracht aan de Polikliniek Late Effecten Kinderoncologie van het UMC Groningen werd de RAND-36 gebruikt. Dit is een internationaal gebruikte en gevalideerde vragenlijst voor het meten van HRQoL, die bestaat uit acht subschalen. De overlevenden werden verdeeld in twee groepen gebaseerd op de tijd verstreken sinds de diagnose: Groep LF (tijd sinds diagnose 20 jaar of korter, n=129) en Groep VLF (tijd sinds diagnose meer dan 20 jaar, n=184). Gegevens betreffende de diagnose, de behandeling en complicaties zijn verkregen uit de medische dossiers. De late effecten van de vroegere behandeling werden naar ernst gegradeerd met behulp van the Common Terminology Criteria for Adverse Events, versie 3 (CTCAEv3). Behalve voor hogere scores op de subschaal pijn waren er voor de overige subschalen van de RAND-36 geen significante verschillen tussen de LF Groep en een steekproef uit de algemene populatie; VLF patiënten hadden significant lagere scores op de subschalen fysiek functioneren, sociaal functioneren, vitaliteit en algemene gezondheidsbeleving. VLF patiënten hadden significant meer ernstige late effecten (graad 3 en 4)(47.8%) in vergelijking tot LF patiënten (27.9%). Vrouwelijk geslacht en het hebben van psycho- sociale late effecten hebben een negatieve invloed op de kwaliteit van leven. Concluderend hebben overlevenden die meer dan 20 jaar geleden behandeld zijn voor kinderkanker meer ernstige late effecten van de behandeling en een slechtere HRQoL in vergelijking met overlevenden die recenter zijn behandeld. Deze bevindingen suggereren ook dat er geen plateau lijkt te bestaan in het voorkomen van late effecten, hoewel longitudinaal onderzoek nodig is om dat met zekerheid te kunnen zeggen.

In **Hoofdstuk 3** hebben wij de gezondheidstoestand van 123 volwassen overlevenden van kinderkanker, gemiddelde leeftijd 33 (19-50) jaar en follow-up duur 27 (9-38) jaar, die teruggeroepen waren in follow-up, onderzocht. De HRQoL van deze 123 overlevenden hebben we vergeleken met een steekproef uit de algemene populatie.

Graad 1-2 late effecten werden gevonden in 54% van de overlevenden en graad 3-4 in 39%; twee of meer late effecten werden gevonden in 70% en in 33% van de overlevenden werden late effecten aangetroffen die voorheen niet bekend waren. Overlevenden hadden significant lagere scores op de subschalen fysiek functioneren, sociaal functioneren, vitaliteit en gezondheidsbeleving van de RAND-36 in vergelijking met de controles. Overlevenden zonder late effecten of met milde late effecten hadden significant hogere scores op de meeste subschalen van de RAND-36 in vergelijking met overlevenden met ernstige late effecten. Onze conclusie was dat bijna 40% van de volwassen overlevenden van kinderkanker getroffen waren door matige tot ernstige late effecten van de vroegere ziekte en behandeling. Bovendien had 33% van de overlevenden late effecten die vooraf niet bekend waren. Daarom is het noodzakelijk om deze oudere overlevenden van kinderkanker terug te roepen voor follow-up controles.

In **Hoofdstuk 4** onderzochten wij hoe het gesteld is met de kennis van ziekte, behandeling en

potentiële late effecten bij volwassen overlevenden van kinderkanker. In de periode 2004-2006 werd aan alle volwassen patiënten van de Polikliniek Late Effecten Kinderoncologie (PLEK poli) gevraagd een vragenlijst in te vullen met tien vragen betreffende kennis over ziekte, behandeling en late effecten. De patiënten werden verdeeld in een Groep Recalled (overlevenden die niet eerder op de PLEK poli gezien waren) en een Groep Regular (overlevenden die al regelmatig voor controle op de PLEK poli kwamen). Een totale kennisscore (TKS) werd berekend als een percentage van het maximale aantal te geven goede antwoorden. Honderdzesentachtig van de195 (95.4%) van de deelnemers vulden een vragenlijst in. Honderdzevenenzestig van deze 186 (89.9%) wisten een omschrijving te geven van hun vroegere ziekte, en slechts 107 (57.5%) wisten de precieze diagnose. Van diegenen die met radiotherapie waren behandeld in het verleden wisten 77/107 (71.9%) het bestralingsveld, van diegenen die een operatie hadden ondergaan wisten60/80 (75%) welke operatie, van diegenen die behandeld waren met chemotherapie waren er maar twee die de namen van de verschillende chemotherapeutica wisten te benoemen. De TKS in deelnemers uit Groep Regular was hoger in vergelijking tot deelnemers uit Groep Recalled (83.3% versus 71.4% p=0.026). Ook waren de deelnemers uit Groep Regular zich meer bewust van het risico op eventuele late effecten in de toekomst in vergelijking tot deelnemers uit Groep Recalled. Een hogere TKS was positief gerelateerd aan een beter bewustzijn van het risico op eventuele late effecten in de toekomst ($p<0.0005$). Reguliere patiënten van de PLEK poli hadden hogere TKS en waren zich meer bewust van het risico op late effecten in vergelijking met patiënten die waren teruggeroepen voor follow-up en voor het eerst de PLEK poli bezochten. Hoewel reguliere patiënten een betere TKS hadden zijn er ook bij hen nog steeds opmerkelijke kennis tekorten.

In **Hoofdstuk 5** onderzochten wij de resultaten van een eenvoudig beweging stimuleringsprogramma aan huis met feedback van een stappenteller op vermoeidheid bij volwassen overlevenden van kinderkanker. Vermoeidheid kan soms lang na het beëindigen van de behandeling voorkomen met een negatief effect op de kwaliteit van leven. De huidige revalidatie programma's die zich onder meer richten op het stimuleren van bewegen hebben een positief effect op de vermoeidheid maar zijn erg intensief en tijdrovend; dit maakt deze programma's minder geschikt voor jonge overlevenden van kinderkanker die aan het begin staan van hun carrière of een jong gezin hebben.

De deelnemers werden geselecteerd uit bezoekers van de PLEK poli van het UMC Groningen. Inclusie criterium was een score van ≥ 75mm op de Visueel Analoge Schaal (VAS; schaal 0-100 mm) voor vermoeidheid. Zevenenzestig deelnemers voldeden aan de inclusiecriteria, 21 wilden niet meedoen, 46 deelnemers begonnen aan de studie en 38 deelnemers volbrachten de studie. Er was een controle groep van 33 gezonde broers, zussen, vrienden of vriendinnen. De deelnemers kregen adviezen van een counsellor die erop gericht waren om op eenvoudige wijze hun lichamelijke activiteiten uit te

breiden. Vermoeidheid werd gemeten met een vermoeidheidsvragenlijst, de Checklist Individual Strength (CIS), die werd afgenomen aan het begin (T0), na 10 weken (T10) en na 36 weken (T36) bij zowel deelnemers als controles. Het dagelijkse aantal stappen werd geregistreerd in een (online) stappen dagboek aan het begin, na 4 en na 10 weken in de deelnemersgroep. De gemiddelde CIS score van de deelnemers was significant verbeterd na de interventie (T10) en deze verbetering was nog steeds significant na 36 weken (T36). Tevens was er een significante toename van het aantal stappen in de deelnemersgroep na de interventie (T10) ($p<0.001$).

Concluderend kunnen we zeggen dat een simpel bewegingsstimuleringsprogramma aan huis met hulp van een counsellor en feedback van een stappenteller gedurende 9 weken een significante verbetering geeft in ervaren vermoeidheid gemeten met de CIS. Deze verbetering is na 36 weken nog steeds significant.

In **Hoofdstuk 6** onderzochten wij de bereidheid van huisartsen, die een nascholing hadden gevolgd over late effecten, om mee te doen aan een samenwerkingsmodel voor de lange termijn controles van volwassen overlevenden van kinderkanker.

Lange termijn follow-up voor overlevenden van kinderkanker wordt op dit moment voornamelijk georganiseerd door kinderoncologen en huisartsen zijn hier zelden bij betrokken. Om langdurige follow-up controles te garanderen voor alle overlevenden van kinderkanker zou de samenwerking van kinderoncologen en huisartsen een oplossing kunnen bieden. Tevens inventariseerden wij welke behoeften huisartsen hebben voor een dergelijke samenwerking en welke bedenkingen een rol spelen.

Driehonderdachtenvijftig huisartsen uit de regio Noord- Nederland deden mee aan een nascholing over late effecten van de behandeling voor kinderkanker. Na de cursus werd hun gevraagd een vragenlijst in te vullen bestaande uit tien vragen betreffende hun motivatie om deel te nemen aan een samenwerkingsmodel voor de lange termijn follow-up van volwassenen die genezen zijn van kinderkanker. De respons was 65%. Zevenennegentig procent van de huisartsen was bereid om mee te doen in het samenwerkingsmodel.

De belangrijkste vereisten voor samenwerking waren de beschikbaarheid van richtlijnen (64%), voldoende informatie over de medische voorgeschiedenis (37%) en korte overleglijnen met de kinderoncologen (45%). De belangrijkste barrières om mee te doen waren werkbelasting (16%), gebrek aan kennis (15%) en gebrek aan communicatie (13%).

Een grote meerderheid van de deelnemende huisartsen was bereid om deel te nemen aan een samenwerkingsmodel voor de lange termijn controles van volwassenen die genezen zijn van kinderkanker indien adequate richtlijnen en informatie over de medische voorgeschiedenis beschikbaar zou zijn. Ongeveer 64% (150/233) huisartsen vond dat deelnemen aan lange termijn controles voor volwassen overlevenden van kinderkanker tot het normale takenpakket van de huisarts behoort.

In **Hoofdstuk 7** beschrijven wij een 3 jarige studie naar de haalbaarheid van een

samenwerkingsmodel waarin kinderoncologen samenwerken met de eigen huisarts van patiënt in de lange termijn follow-up van volwassen overlevenden van kinderkanker.
Wij hebben onderzocht of een samenwerkingsmodel, waarin kinderoncologen en huisartsen samenwerken aan de lange termijn follow-up voor volwassenen die genezen zijn van kinderkanker, haalbaar is. Voorafgaand aan het bezoek werd de huisarts van de patiënt geïnformeerd over de mogelijke gezondheidsrisico's en kreeg hij/zij de richtlijn voor follow-up afgestemd op zijn/haar patiënt. De huisarts werd verzocht om de informatie betreffende de controle en de uitgevoerde testresultaten terug te sturen naar de Polikliniek Late Effecten Kinderoncologie (PLEK) poli van het UMCG.
Wij hebben nagegaan of een dergelijk samenwerkingsmodel verenigbaar is met het verzamelen van de data die nodig zijn voor de registratie van late effecten en hebben gekeken naar de tevredenheid van zowel huisartsen als patiënten met dit model.
De deelnemers bezochten in jaar 1 en in jaar 3 de PLEK poli in het UMCG alwaar zij gezien werden door een coördinerende huisarts verbonden aan de afdeling kinderoncologie. In het tussenliggende jaar (jaar 2) werden zij gecontroleerd door hun eigen huisarts. Honderddrieentwintig van de 133 (92%) patiënten die we benaderden voor deze studie deden mee en 115 van de 117 (98%) van de gevraagde huisartsen. Honderddrie van de 115 (90%) deelnemende huisartsen stuurden gegevens van de betreffende controle naar de PLEK poli. Aan het einde van de studie werd de tevredenheid van patiënten en huisartsen bepaald aan de hand van vragenlijsten. Negenentachtig van de 101 (89%) patiënten die de vragenlijst terugstuurden waren tevreden en 94 van de 115 (82%) huisartsen waren tevreden. We concludeerden dat een samenwerkingsmodel voor de lange termijn controles van volwassen overlevenden van kinderkanker uitvoerbaar is.
In de discussie **Hoofdstuk 8** bediscussiëren wij de verschillende modellen voor follow-up. We inventariseren de vragen en de controverses aangaande de rol van de huisarts in de lange termijn follow-up en doen aanbevelingen voor de toekomst.
Onze conclusie is dat een 'shared care' model uitvoerbaar is voor de lange termijn follow-up van volwassenen die genezen zijn van kinderkanker. Men zou kunnen stellen dat follow-up 'op maat gesneden' moet zijn voor de individuele overlever en daarom zal meer dan één model nodig zijn. Modellen moeten flexibel zijn en zich kunnen aanpassen aan de diverse levensfasen; jonge kinderen hebben andere behoeften dan (jong) volwassenen. Follow-up moet gebaseerd zijn op het individuele risico op het krijgen van late effecten en bij overlevenden met geen of een laag risico moet follow-up door middel van vragenlijsten of telefonische interviews overwogen worden. Ook de eigen wensen en ideeën ten aanzien van lange termijn follow-up moeten meegenomen worden in de keuze voor follow-up; deze wensen kunnen veranderen met het ouder worden. Alleen op deze manier kan men er voor zorgen dat overlevenden van kinderkanker blijven komen

voor follow-up controles. Dit is belangrijk omdat veel late effecten pas vele jaren na het beëindigen van de therapie kunnen optreden.

Dankwoord

Toen ik besloot te solliciteren op de vacature "zorgketenbenadering voor de lange termijn follow-up van 'genezen' kinderen met kanker", stond promoveren zeker niet op mijn verlanglijstje. Liedeke Postma, mijn copromotor en vaste begeleider, heeft mij in de loop der tijd kunnen overtuigen van het feit dat promoveren nuttig kan zijn om een onderwerp wat je aan het hart gaat in de schijnwerpers te plaatsen.

Het is belangrijk dat huisarts en specialist meer naar elkaar toegroeien. Lang hebben beide beroepsgroepen zich gefocust op hun eigen problemen. Maar huisartsen en specialisten hebben elkaar hard nodig als ze samen de sterk stijgende zorgvraag willen opvangen en de gezondheidszorg betaalbaar willen houden. Ik hoop dat dit proefschrift een bijdrage kan leveren aan een betere samenwerking tussen huisartsen en specialisten in het algemeen en aan een betere samenwerking voor de zorg voor kinderen die zijn 'genezen' van kanker in het bijzonder.

Nu het proefschrift klaar is rest mij een ieder te bedanken die zich heeft ingezet om dit voor elkaar te krijgen. Allereerst wil ik de patiënten en huisartsen die hebben deelgenomen aan de onderzoeken uit dit proefschrift bedanken voor hun deelname. Dit proefschrift was er niet geweest zonder hun medewerking!

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Curriculum vitae

Ria Blaauwbroek werd op 19 september 1961 geboren in Heerlen. Na de middelbare school (Atheneum-B, Oosterwolde) studeerde zij geneeskunde aan de Rijksuniversiteit van Groningen. Na het behalen van het artsexamen volgden arts-assistentschappen interne, chirurgie en gynaecologie in het Diaconessenziekenhuis Groningen en het Medisch Centrum Leeuwarden als voorbereiding op een uitzending naar de tropen. Van 1990-1993 werkte zij samen met haar man in het Huruma ziekenhuis in Tanzania. Inmiddels moeder geworden van Niels(1989), Lara(1990) en Thom(1993) begon zij in 1994 aan de huisartsopleiding. Na het einde van de huisartsopleiding vestigde zij zich in een groepspraktijk in Buitenpost. Sinds 2004 is zij twee dagen per week verbonden aan de afdeling kinderoncologie van het Universitair Medisch Centrum Groningen om een 'shared care' model voor de lange termijn follow-up voor volwassen overlevenden van kinderkanker op te zetten.

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